ON HAVING NO BETA-LIPOPROTEIN
A SYNDROME COMPRISING A-BETA-LIPOPROTEINÆMIA, ACANTHOCYTOSIS, AND STEATORRHŒA

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A NEW syndrome comprising an abnormal appearance of the red blood-cells, retinopathy, and disease of the central nervous system was first described by Bassen and Kornzweig (1950). They reported the disease in a Jewish girl, aged 18 years, whose parents were first cousins. The neurological disorder was thought to involve the posterior columns, the pyramidal tracts, and the cerebellar pathways. The retinopathy presented the appearance of an atypical retinitis pigmentosa with involvement of the macula; and the red cells showed pseudopodia of irregular length and number, which gave them a crenated appearance. These workers found that the patient's younger brother had the same anomalies, and later they published a full account of his disorder at the age of 18 (Kornzweig and Bassen 1957). The red-cell abnormality had persisted, the retinitis pigmentosa, which was first noticed at the age of 9, had progressed, and an ataxic neuropathy, which was first observed at 11 years, had developed further.

Singer et al. (1952) reported the case of a $13^1/_2$-year-old boy, whose parents were second cousins, who had a progressive ataxic neuropathy and whose blood showed this same abnormality of the red cells. There was no retinopathy. These workers named the red cells acanthrocytes (*acanthus*=thorn or sharp point), and they showed that the red cells had a slightly decreased osmotic fragility, but a considerably increased lysolecithin and mechanical fragility. They suggested that the acanthrocytosis was genetically conditioned, and was due to a mutant recessive allele for a gene controlling the normal architecture of the red cell. Jampel and Falls (1958) gave a further description of this patient, then aged 19. Retinopathy had developed and the neurological lesion had progressed to incapacity.

Another case of acanthocytosis* was described by Druez (1959) in a woman aged 30, whose grandparents were first cousins but whose parents were unrelated, and who showed a non-pigmentary retinitis with choroiditis. She is said to have been ataxic from the age of 2 years.

These four patients are reported to have had the cœliac syndrome:

In the first patient the disorder developed at the age of 2 years and is said to have regressed at 12 years, but at the time of the case-report, when she was 18 years old, she was only 5 ft. tall, with thin extremities, and she looked much younger than her age.

In her brother cœliac disease was diagnosed at 9 months, but it improved after a year of therapy.

Cœliac disease was first diagnosed in the third patient in infancy; and when he was investigated again at the age of 19 steatorrhœa was still present. His total serum-cholesterol was then 37 mg. per 100 ml., the cholesterol ester being 23 mg. and free cholesterol 14 mg. Electrophoresis of the serum-proteins showed a low γ-globulin and a low β-globulin.

Druez's patient had had diarrhœa in infancy, and at the age of 30 she was very thin, she had episodes of diarrhœa, and she complained of "fat intolerance". The serum-cholesterol was 60 mg. per 100 ml.

In our patient, now to be described, the investigation of the defective fat absorption and transport makes it possible for us to enlarge the previous concept of this syndrome.

Case-report

A female infant born on Jan. 28, 1958, after a normal pregnancy and confinement, was the only child of unrelated healthy parents. At 5 weeks she began vomiting after feeds and occasionally passed loose yellow stools. At 7 weeks she was admitted to hospital. She was pale and wasted (1 oz. below her birthweight), with some abdominal distension and a few bruises over the sacrum. The only abnormalities detected on investigation were a low serum-globulin (1·3 g. per 100 ml.) with a normal distribution of the globulin fractions on paper electrophoresis, and an increased prothrombin-time which responded promptly to intramuscular vitamin K. Her progress was slow, but she was discharged home well at 4 months.

Fig. 1—The patient, aged 17 months.

Subsequent progress was only moderately satisfactory; occasional episodes of vomiting and loose stools, together with abdominal distension, persisted. At 9 months, because of an acute attack of vomiting and diarrhœa with fever, she was readmitted to hospital. There were no abnormal signs, but the stools were pale and fluid, and contained mucus from which no pathogenic organisms were isolated. The peripheral blood showed anæmia, with a hæmoglobin of 9·7 g. per 100 ml. and anisocytosis, poikilocytosis, and hypochromia. The acute symptoms settled rapidly and she was discharged after a week. Thereafter intermittent diarrhœa continued, with the passage of bulky loose pale offensive stools—this abnormality persisting between the acute attacks of diarrhœa. She remained well nourished, and her temperament was happy and equable.

* We agree with Druez that this disorder is more correctly named acanthocytosis, not acanthrocytosis, and we shall use this term throughout.

SERUM-LIPIDS AND LIPOPROTEINS IN THE PATIENT AND THE AFFECTED MEMBERS OF HER FAMILY

Subject	Patient	Affected relatives			Normal range
		Mother	Father	Paternal grandfather	
Age (yr.)	1¼	30	32	59	
Serum lipids:					
Total lipid (mg. per 100 ml.)	80	460	460	670	470–860
Cholesterol "	22	127	107	154	120–250
Phospholipid "	45	142	139	..	160–310
Vitamin A (I.U. per 100 ml.)	19	110	82	177	80–180
Carotenoid (μg. per 100 ml.)	0	84	68	47	60–260
Unesterified fatty acid (mEq. per l.) Fasting	1·0	..	..	..	0·4–1·2
3½ hr. after fat meal*	0·3	..	..	..	..
Chylomicrons after fat-meal	Absent	Present	Present	..	Present
Serum lipoproteins:					
α-lipoprotein† (mg. per 100 ml.)	80	211	228	270	150–280
β-lipoprotein† "	0	216	149	289	300–580
Ratio: β/α "	0	1·0	0·7	1·1	1·5–3·0
β-lipoprotein‡ (per cent of a normal control)	0	50	50	..	..
Ultracentrifugal fractions:					
Low density Sf 0–400:					
Cholesterol (mg. per 100 ml.)	0	72	60	..	100–200
Phospholipid "	0	83	64	..	110–200
High density:					
Cholesterol "	19	46	41	..	30– 60
Phospholipid "	38	65	65	..	50–110
β-lipoprotein (by analytical ultracentrifuge)	Absent	Reduced	..	..	Present

* This reduction in unesterified-fatty-acid concentration represents a normal response to the carbohydrate content of the meal.
† As lipid, by paper electrophoresis. ‡ As protein, by immunochemical assay.

At 17 months she was again admitted to hospital with a provisional diagnosis of cœliac disease. Her weight was 24 lb. and her height 30¼ in. The abdomen was distended and the buttocks wasted (fig. 1). The retinæ (Mr. M. J. Roper-Hall) and the nervous system were normal.

INVESTIGATIONS

The persistent finding of clear pale serum with a total-cholesterol level of 19–25 mg. per 100 ml. led to detailed studies of fat absorption and lipid transport. The results of the serum investigations are given in the table.

Serum-total-lipid was estimated by the method of de la Huerga et al. (1953), total cholesterol by the method of Sackett (1925), and phospholipid (lipid phosphorus × 26) by a method adapted from Gomori (1942). Lipoproteins were determined by paper electrophoresis (Salt and Wolff 1957) and by ultracentrifugation using the salt-density method of fractionation. The results were confirmed with the analytical ultracentrifuge using flotation of β-lipoprotein in a medium of density 1·065, and of all lipoproteins in media of density 1·246 and 1·360. By an immunochemical technique (Gell 1957), using a specific rabbit antiserum to human β-lipoprotein, it was established that the concentration of this protein was less than 1/1000 of its concentration in the serum of a healthy adult. Serum-vitamin-A and carotenoids were estimated by the methods of Campbell and Tonks (1949), and unesterified fatty acid by the method of Grossman et al. (1954).

Absorption of particulate fat (chylomicrons) was studied by measurements of serum turbidity using 370 mμ wavelength. In these experiments a meal containing approximately 1 g. fat per lb. body-weight was given, and serial estimations of turbidity and total lipid were made for 6 hours. In the normal person, maximal turbidity appears about 3½ hours after ingestion of the fat. In our patient there was no turbidity or rise in total lipid at any time, irrespective of whether the fat was given as animal fat or corn oil.

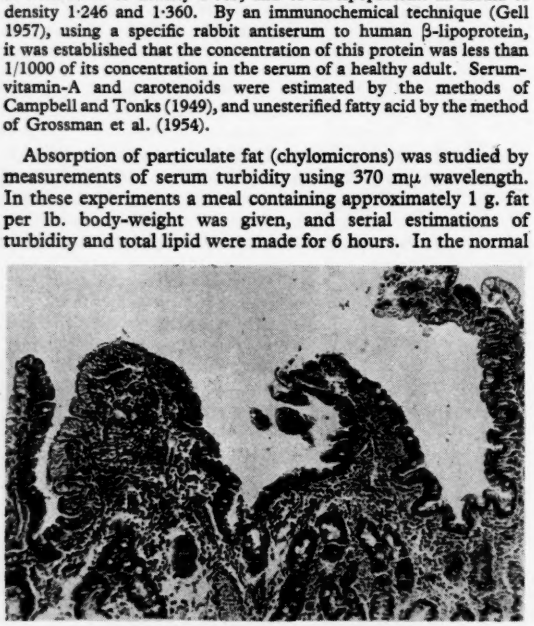

Fig. 2—Jejunal biopsy, low power (H.& E.).
The villi are distinct but irregular in shape and size.

Daily estimations of fæcal-fat content were made on 43 occasions, and the mean daily output was 6·7 g. (the normal daily fæcal fat does not exceed 4·5 g.). The steatorrhœa was uninfluenced by a gluten-free diet given for 10 weeks. No pathogenic organisms, cysts, or ova were found in the fæces. Glucose-tolerance tests, with both oral and intraduodenal administration of glucose, showed maximal rises of 37 and 33 mg. per 100 ml. respectively. The duodenal contents contained a normal concentration of bile acids (1·7 mg. per ml., estimated by an adaptation of the method of Chabrol et al. (1934), and showed adequate lipolytic and tryptic activity. The sodium and chloride concentrations in the sweat were normal (13 and 21 mEq. per litre respectively).

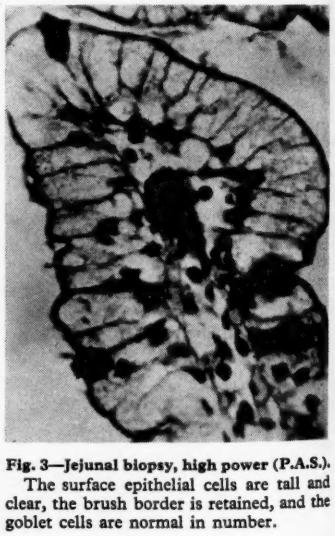

Fig. 3—Jejunal biopsy, high power (P.A.S.).
The surface epithelial cells are tall and clear, the brush border is retained, and the goblet cells are normal in number.

Jejunal biopsy showed an abnormal appearance which was quite unlike that seen in our own experience of cœliac disease or that described by Shiner (1957), Fone et al. (1960), and Rubin et al. (1960). The lamina propria was of normal thickness and cellularity, and contained a normal complement of plasma-cells. The villi were well defined but slightly irregular (fig. 2). The columnar cells covering the surface of the villi had unusually clear cytoplasm which did not stain with periodic-acid-Schiff (fig. 3).

A barium-meal (Dr. Roy Astley) showed the dilated appearances of the small intestine usually associated with cœliac disease (Anderson et al. 1952). The bone-age was normal.

The serum albumin was 4·8 and the globulin 2·1 g. per 100 ml., and electrophoretic separation of proteins showed slight

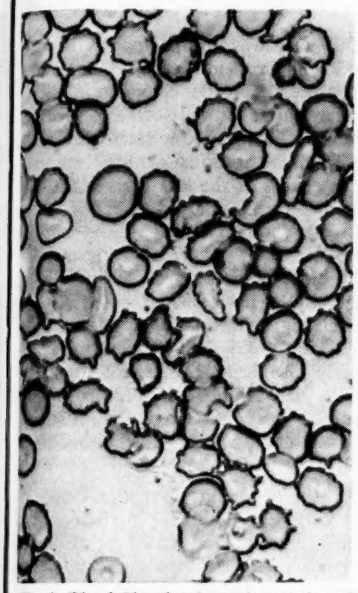

Fig. 4—Blood-film showing anisocytosis and several acanthocytes (Leishman).

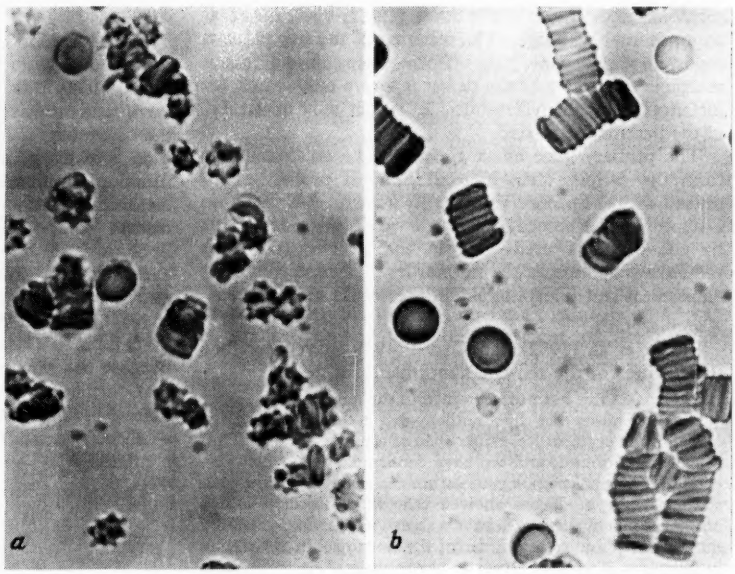

Fig. 5—Wet preparations of blood: (a) showing acanthocytes and absence of rouleaux formation in the patient; (b) showing normal red cells and rouleaux formation in the mother.

depletion of all globulin fractions (α_1 0·3, α_2 0·7, β 0·75, and γ 0·35 g. per 100 ml. serum). Immunochemical determinations showed normal levels of albumin, siderophilin, cæruloplasmin, α_1-glycoprotein, and a component of complement (probably C'_1), with serum γ-globulin 0·48 g. per 100 ml. serum. Serum calcium was 9·7 and phosphorus 6·2 mg. per 100 ml., and the alkaline phosphatase was 7 King-Armstrong units. Urinary aminoacids were normal.

The hypochromic microcytic anæmia was persistent. The hæmoglobin was 9·7 g. per 100 ml., the red-cell count 5·4 million per c.mm., the packed-cell volume 32%, the mean corpuscular volume 60 c.μ, and the mean corpuscular-hæmoglobin concentration 30%. The total and differential leucocyte counts and the platelet count were normal. The red cells showed much anisocytosis, poikilocytosis, and hypochromia (fig. 4). Target cells were fairly numerous, and there was some polychromasia. Many cells had a serrated margin with a cog-wheel appearance characteristic of acanthocytosis. Wet preparations taken directly from a finger-prick showed about 50% acanthocytes and no rouleaux formation (fig. 5[*a*]). Acanthocytosis persisted when washed red cells were suspended in normal homologous serum. The erythrocyte-sedimentation rate (Wintrobe) was reduced, with a corrected fall of less than 1 mm. in the 1st hour. The red-cell fragility was decreased in saline, hæmolysis beginning at 0·44 g. per 100 ml. and not being complete until 0·2 g. per 100 ml. The serum-iron (75 μg. per 100 ml.) was slightly reduced, and the serum-vitamin-B_{12} (175 $\mu\mu$g. per ml.) was normal. The Kahn and Wassermann reactions were negative, and the blood-group was O, Rh-positive. Analysis of the red-cell lipids (Boyd 1936) showed a normal intracorpuscular concentration of cholesterol (202 mg. per 100 ml. red cells) and phospholipid (338 mg. per 100 ml. red cells). No abnormal hæmoglobin was detected by electrophoresis. An electroencephalogram was normal.

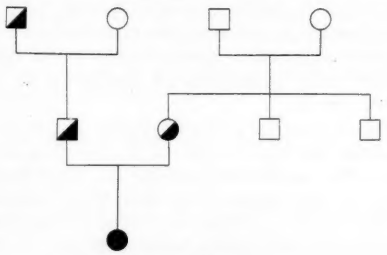

Fig. 6—Family tree.
Squares = male. Circles = female.
Full-shaded = homozygote (absence of β-lipoprotein and presence of acanthocytes).
Half-shaded = heterozygote (reduced β-lipoprotein).

In summary, the investigations showed steatorrhœa associated with absence of chylomicrons (the serum remaining clear even after a fat-meal), absence of β-lipoprotein with correspondingly low levels of cholesterol, phospholipid, and total lipid, and acanthocytosis of the red cells.

TREATMENT

Treatment of the steatorrhœa by a gluten-free diet for 10 weeks failed to improve fat absorption. Later, a low-fat diet (20 g. daily) resulted in weight gain, considerable improvement in general condition, and cessation of diarrhœa. The hypochromic anæmia responded to intramuscular iron dextran; the hæmoglobin rose to 13·1 g. per 100 ml. Water-soluble vitamin A (20,000 units daily) raised the serum-vitamin-A level to normal (108 I.U. per 100 ml.), but the carotenoids remained absent.

FINDINGS IN RELATIVES

We were able to investigate the grandparents, the parents, and the two uncles of our patient. None of these had neurological symptoms or retinitis, and blood films (fig. 5[*b*]) and osmotic fragilities were normal. The serum lipids were abnormal in both parents and in the paternal grandfather (see table and fig. 6), the β-lipoprotein being about half the mean normal, with corresponding reduction of total lipid, cholesterol, phospholipid, and the β/α lipoprotein ratio. In the other relatives the serum-lipids were normal. Chylomicron absorption after a fat-meal, studied only in the parents, was normal. Four children of one of the uncles were not examined, and are omitted from the family tree; they were said to be in good health.

Discussion

This condition, which we propose to call *a-β-lipoproteinæmia*, apparently arises from an inborn error of

metabolism in which the mutant gene is transmitted as an autosomal recessive. The fact that of the five patients reported three were the offspring of consanguineous marriage suggests that the defect is a rare one—rarer, for instance, than phenylketonuria in which only about 8% of the parents are related.

The primary gene effect appears to be an inability to form the β-lipoprotein molecule, and is probably concerned with the protein moiety. As a result, β-lipoprotein is absent in the homozygote—or at least is not detectable by the methods used—and in the heterozygote it is reduced to about half the normal level. Correspondingly cholesterol and phospholipid in the serum are reduced.

Acanthocytosis

Singer et al. (1952) and Druez (1959) have described the features of the red-cell abnormality in detail.

In all cases this has been confined to the homozygote. Some evidence suggests that the acanthocytosis is due to an intrinsic defect of the erythrocytes rather than to a plasma factor. Thus Singer et al. found, and we have confirmed, that when suspended in normal homologous serum acanthocytes retain their abnormal shape. Druez showed that when injected into a normal recipient these cells have a shortened survival-time. Of the intracorpuscular constituents, the hæmoglobin was found by Singer et al. and by Druez to have a normal electrophoretic mobility, and we have confirmed this. Druez suggests that acanthocytosis may result from an abnormal structure of the red-cell membrane or from an abnormal binding of the lipoprotein molecules to the underlying hæmoglobin.

There are two further hypotheses which could link the a-β-lipoproteinæmia and acanthocytosis: (1) possibly a missing enzyme, which is responsible for the absence of β-lipoprotein from the plasma, may also interfere with the formation of a protein or lipoprotein essential for normal red-cell structure; or (2) β-lipoprotein may be essential for the transport of some substance needed for synthesis of the red-cell envelope.

Ataxia and Atypical Retinitis Pigmentosa

In Druez's patient the ataxia dated from early childhood; in the other patients the disabling ocular and neurological disturbances did not appear until the later years of childhood or adolescence. Singer et al. regarded the ataxia and the atypical retinitis pigmentosa as abiotrophic disorders—i.e., hereditary conditions which may remain latent for many years. On the other hand, Jampel and Falls (1958) thought the entire syndrome was due to an inborn error of fat metabolism producing secondary harmful effects on the erythrocytes and nerve-cells.

On the whole we favour Singer's view that the ocular and nervous disturbances are genetically determined, and we speculate that a factor essential for the production of β-lipoprotein is also essential for the normal structure and function of nerve-cells. But the possibility that these disturbances result from disordered fat absorption and transport cannot be completely ruled out. Absorption of vitamin A is impaired whenever chylomicron absorption is interfered with; and the carotenoids, the precursors of vitamin A, are normally carried in plasma by β-lipoprotein. It is therefore not surprising that in our patient serum levels of vitamin A were low and carotenoids absent; and it is conceivable that prolonged severe vitamin-A deficiency could play a part in the causation of the ataxia and retinopathy. Administration of water-soluble vitamin A raised our patient's serum level to normal, and only time will show whether in this way the distressing neurological features of the syndrome can be prevented.

Steatorrhœa

The symptoms of the cœliac syndrome appeared before the age of 2 years in all four previous cases. Our patient had bruising due to prothrombin deficiency at 7 weeks. As treatment with vitamin K intramuscularly corrected the deficiency, it seems probable that the steatorrhœa was then already present. Investigations of her intestinal function eliminated as causes of the steatorrhœa the two conditions commonly met in pædiatric practice: fibrocystic disease of the pancreas was excluded by the normal lipolytic and tryptic activity, and cœliac disease was excluded by jejunal biopsy, by lack of response to a gluten-free diet, and by a normal glucose-absorption curve. Bile-acid deficiency, a rare cause of steatorrhœa in childhood (Ross et al. 1955), had to be considered because the remarkably low serum-cholesterol suggested that formation of bile acid from cholesterol might be defective. This condition was ruled out by the finding of a normal concentration of bile acid in the duodenal contents.

The outstanding feature of the fat-absorption defect in our patient was the complete failure of particulate fat (chylomicrons) to appear in the blood after a fat-meal. In the presence of adequate pancreatic lipase and bile acid in the duodenal contents, this failure is unlikely to result from incomplete intraluminar emulsification. Therefore the finely emulsified water-insoluble lipid should have penetrated into the outer border of the intestinal lining cells. These cells are known to be metabolically active (Frazer 1958), one of their functions being the formation of chylomicrons from triglyceride, phospholipid, and protein. Until exact knowledge of the protein moiety of chylomicrons and other lipoproteins is available, three alternative hypotheses could explain the absence of chylomicrons from our patient's serum:

1. An enzyme essential for the formation of β-lipoprotein may likewise be essential for the formation of chylomicrons.

2. The presence of β-lipoprotein within the cell may be necessary for the formation of chylomicrons from triglyceride. This does not necessarily imply identity between the proteins of the two lipoprotein groups; in fact, Rodbell (1958) has adduced evidence by determination of N-terminal aminoacid groups that these proteins differ, whereas the protein constituents of α-lipoprotein and chylomicrons may be identical.

3. The presence of β-lipoprotein in plasma may be necessary for the maintenance of a chylomicron emulsion.

Thus if chylomicrons cannot be formed in the lining cells or transported in the chyle and blood, one might expect triglyceride to accumulate in the lining cells. Here it is tempting to speculate that the appearance of lining cells with an unusually clear cytoplasm results from accumulation of water-insoluble lipid particles. Unfortunately our biopsy material was insufficient for fat staining. Such triglyceride accumulation would then interfere with further absorption of particulate fat from the intestinal lumen.

As well as absence of β-lipoprotein and chylomicrons, our patient showed considerable depletion of α-lipoprotein. The explanation may be that high-density lipoproteins are maintained by lipolysis of chylomicrons. We have seen similar depletion in patients with other forms of steatorrhœa associated with defective chylomicron absorption.

Although in our patient the principal mode of fat absorption appeared to be completely unavailable, there was an overall absorption of dietary fat of about 87%.

Diagnosis

The diagnosis of a-β-lipoproteinæmia should be suspected in a patient with steatorrhœa associated with a very low serum-cholesterol, for we know of no other condition in which such low levels occur. The absence of β-lipoprotein from the serum can then be confirmed by electrophoretic and immunochemical methods, or by ultracentrifugation.

To recognise the acanthocytes it is essential to examine fresh undiluted blood, when the typical spiky appearance of the majority of the red cells, and their failure to form rouleaux, will be obvious. In the stained film the abnormality is easily mistaken for crenation, and similarly in fresh blood diluted with saline the acanthocyte cannot be differentiated from a crenated red cell. The very low erythrocyte-sedimentation rate merely confirms the failure of rouleaux formation.

Bassen and Kornzweig (1950), Singer et al. (1952), and Jampel and Falls (1958) suggest that the syndrome should be suspected in cases of atypical retinitis pigmentosa and Friedreich-like ataxia. Such patients will usually have reached the later years of childhood or adolescence and we expect that the characteristic abnormalities of the serum-lipids will be demonstrable, and that steatorrhœa will still be present.

Summary

A 17-month-old girl with steatorrhœa was found to have no serum β-lipoprotein, with corresponding lowering of cholesterol (22 mg. per 100 ml.) and phospholipid (45 mg. per 100 ml.). No particulate fat (chylomicrons) appeared in the plasma after a fat meal, plasma-vitamin-A was grossly deficient, and the carotenoids were absent. Further investigation of the steatorrhœa excluded cœliac disease and fibrocystic disease of the pancreas. The red blood-cells showed the phenomenon of acanthocytosis.

In the parents and one grandparent the β-lipoprotein was reduced to about half its normal level. The syndrome, which we designate a-β-lipoproteinæmia, is regarded as an inborn error of metabolism with a recessive mode of inheritance.

Possible relationships are discussed between the absence of β-lipoprotein, the red-cell abnormality, and the steatorrhœa.

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REFERENCES

Anderson, C. M., Astley, R., French, J. M., Gerrard, J. W. (1952) *Brit. J. Radiol.* **25**, 526.
Bassen, F. A., Kornzweig, A. L. (1950) *Blood*, **5**, 381.
Boyd, E. M. (1936) *J. biol. Chem.* **115**, 37.
Campbell, D. A., Tonks, E. L. (1949) *Brit. med. J.* ii, 1499.
Chabrol, E., Charonnat, R., Cottet, J., Blonde, P. (1934) *C. R. Soc. Biol., Paris*, **115**, 834.
de la Huerga, J., Yesinick, C., Popper, H. (1953) *Amer. J. clin. Path.* **23**, 1163.
Druez, G. (1959) *Rev. Hémat.* **14**, 3.
Fone, D. J., Cooke, W. T., Meynell, M. J., Bewer, D. B., Cox, E. V., Harris, E. L. (1960) *Lancet*, i, 933.
Frazer, A. C. (1958) *Brit. med. Bull.* **14**, 212.

References continued at foot of next column

THE RISKS OF DEFERRING VALVOTOMY IN PATIENTS WITH MODERATE MITRAL STENOSIS

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THE success of mitral valvotomy in relieving symptoms, preventing complications, and prolonging life in suitable cases of mitral stenosis is generally accepted, but some doubt remains as to the right time to advise operation.

There is no difficulty in advising valvotomy in patients with severe breathlessness on exertion due to mitral stenosis, or in withholding operation from those who are symptom-free and in whom the signs suggest that the stenosis is trivial. However, a large number of patients fall into a middle group in which the physical signs suggest moderate stenosis, and yet symptoms are lacking or trivial. How soon should these patients be encouraged to undertake the risks of valvotomy? No prospective controlled trial of surgical and conservative treatment in patients with moderate mitral stenosis and trivial symptoms has been reported. In the present paper the results of deferring valvotomy in this group of patients are described in order to serve as a retrospective control study providing information of value in deciding the right time to advise valvotomy in such patients.

Method

Material

The present study is based on a review of 518 patients with dominant mitral stenosis seen at the Brompton Hospital and the National Heart Hospital between 1950 and 1959. In 114 of these patients the mitral valve was estimated on clinical grounds to be anatomically suitable for valvotomy but operation was deferred because symptoms were trivial or absent.

The initial assessment of the patients and the decision to defer operation was made by the physicians in charge (Dr. Paul Wood in 111 cases and Dr. R. V. Gibson in 3 cases). After deferment the patients attended hospital, usually at intervals of six months, and during the period of this study (1957–59) they were as far as possible seen by the author. Those who failed to keep hospital appointments were visited at home and 106 patients were successfully traced and assessed; of the remaining 8 patients who were untraced, 5 had left the country. During the follow-up period 1 patient died from carcinoma of the stomach at a time when her symptoms from mitral stenosis were trivial. She was excluded from the analysis because she did not contribute information relevant to the risk of deferring valvotomy.

Criteria for Selection of Patients

The analysis is based on 105 patients. All had dominant mitral stenosis of moderate severity and were assessed

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Gell, P. G. H. (1957) *J. clin. Path.* **10**, 67.
Gomori, G. (1942) *J. Lab. clin. Med.* **27**, 955.
Grossman, M. I., Palm, L., Becker, G. H., Moeller, H. C. (1954) *Proc. Soc. exp. Biol., N.Y.* **87**, 312.
Jampel, R. S., Falls, H. F. (1958) *A.M.A. Arch. Ophthalmol.* **59**, 818.
Kornzweig, A. L., Bassen, F. A. (1957) *ibid.* **58**, 183.
Rodbell, M. (1958) *Science*, **127**, 701.
Ross, C. A. C., Frazer, A. C., French, J. M., Gerrard, J. W., Sammons, H. G., Smellie, J. M. (1955) *Lancet*, i, 1087.
Rubin, C. E., Brandborg, L. L., Phelps, P. C., Taylor, H. C. (1960) *Gastroenterology*, **38**, 28.
Sackett, G. E. (1925) *J. biol. Chem.* **64**, 203.
Salt, H. B., Wolff, O. H. (1957) *Arch. Dis. Childh.* **32**, 404.
Shiner, M. (1957) *J. Mt Sinai Hosp.* **24**, 273.
Singer, K., Fisher, B., Perlstein, M. A. (1952) *Blood*, **7**, 577.

initially on the basis of the history, examination, and special investigations, as described by Wood (1954), whose classification of breathlessness (grades 1–4) was used.

The important feature of the initial history in all patients was the absence of marked breathlessness on exertion. Some were symptom-free and none complained of more than moderate breathlessness on exertion (grade 2).

The physical signs common to all cases were at least moderate accentuation of the first heart-sound in the mitral area and a mitral diastolic murmur of at least moderate intensity and duration. The opening snap, when present, was estimated by auscultation to be not more than moderately close to the aortic second sound in all patients seen after 1953, when the significance of this sign was first appreciated (Wells 1954). An opening snap was not heard in 9 patients, but in 5 of these calcification of the mitral valve was seen on the plain chest X-ray or on fluoroscopy. The presence or absence of fibrillation was not a factor in selecting cases for deferment.

The chest X-ray showed in all patients at least mild left atrial enlargement. There was no right ventricular preponderance on the electrocardiograms and a P-mitrale was present on all except 3 of the electrocardiograms showing sinus rhythm. If there was some discrepancy between the symptoms and signs which still left the severity of the stenosis in doubt after examination of the chest X-ray and electrocardiogram, the patient was submitted to cardiac catheterisation. 30 patients were catheterised before deferment. The mean pulmonary capillary venous pressure was 12 mm. (range 5–18 mm.) A pulmonary capillary venous pressure greater than 15 mm. Hg at rest was taken as evidence of stenosis severe enough to warrant valvotomy in the absence of symptoms, exceptions being made in three borderline cases on the grounds of the youth of the patients.

In 33 patients other valvular lesions in addition to mitral stenosis were detected when the patient was first seen, though in all cases mitral stenosis was thought to be the dominant lesion.

Results

Progress after Deferment

105 patients with dominant moderate mitral stenosis were followed for an average of four and a half years after deferment of valvotomy; valvotomy was advised if a systemic embolus occurred or if the patient developed progressive breathlessness. 6 patients died before operation was advised, all of them following emboli. In 1 case the embolus occurred during an attack of subacute bacterial endocarditis.

Follow-up showed that the patients were likely to take one of four distinct courses and so the patients' progress was classified in retrospect accordingly.

The first course was the development of subacute bacterial endocarditis, which occurred in only 1 patient.

TABLE I—RESULTS OF DEFERRING VALVOTOMY IN 105 PATIENTS

—	Course after deferment				
	Total	Subacute bacterial endo-carditis	"Em-bolic"†	"Pro-gressive"	"Static"
No. of patients	105	1	22	39	43
Length of follow up in years*	3·4	0·3	2·8	3·9	3·4
Fibrillating initially ..	29	0	10	10	9
Developing fibrillation ..	20	0	7	6	7
Developing progressive breathlessness.. ..	45	0	6	39	0
Dying before operation advised	6	1	5	0	0

* Preoperative in cases submitted to operation.
† With or without progressive breathlessness.

The remaining patients were divided into three groups. The first comprised 22 patients who had systemic emboli (not occurring in the course of subacute bacterial endocarditis), whether or not they had the additional symptom of progressive breathlessness on exertion. A second group comprised 39 patients in whom the onset of progressive breathlessness (grade 3) indicated that the mitral stenosis was "critical" and in whom valvotomy was therefore advised: any embolic cases were excluded from this group. A third group comprised the remaining 43 patients in whom there was insufficient change in symptoms to warrant valvotomy. These three goups are for simplicity referrred to as the "embolic", "progressive" and "static" groups (table I):

"*Embolic*" *group.*—In 22 patients systemic emboli occurred after deferment of valvotomy; 5 patients died following emboli and 10 had residual disability. All the deaths followed cerebral emboli of which there were 15. 6 "embolic" patients had progressive breathlessness (grade 3) at the time embolism occurred, and therefore had a double qualification for submission to operation.

"*Progressive*" *group.*—All 39 patients in this group developed progressive breathlessness on exertion. In 19 of them paroxysmal nocturnal dyspnœa, orthopnœa, or pulmonary œdema also occurred. 5 patients developed atrial fibrillation and in 1 patient paroxysmal fibrillation occurred. With increasing breathlessness, the physical signs became more florid with a palpable right ventricular pulsation, a closer and louder opening snap, and a full-length mitral diastolic murmur. Changes of mild "chronic interstitial œdema" appeared on the chest X-rays of 11 patients.

"*Static*" *group.*—None of the 43 patients in this group developed symptoms sufficient to justify valvotomy. Atrial fibrillation occurred in 7 patients in this group and in 2 the rhythm change precipitated an attack of pulmonary œdema. All 7 have since been maintained on digitalis and none has more than trivial breathlessness on exertion.

Retrospective Analysis

The initial clinical features of patients in the three main groups were contrasted in retrospect in an attempt to

TABLE II—CLINICAL FEATURES OF PATIENTS WHEN FIRST DEFERRED

—	No. of patients	Average age	Under age of 40 when first deferred	Fibrillating when first deferred	Without opening snap	Mild mitral incompetence	Mitral-valve calcification
Total*	104	37	54 (*52%*)	29 (*28%*)	9 (*9%*)	16 (*15%*)	7
"Embolic"	22	42	4 (*18%*)	10 (*45%*)	6 (*27%*)	2 (*9%*)	3
"Progressive"	39	37	24 (*62%*)	10 (*26%*)	1	8 (*20%*)	2
"Static"	43	35	26 (*60%*)	9 (*21%*)	2	6 (*14%*)	2

* Excluding the patient with subacute bacterial endocarditis.

discover features which might be associated with the three types of progress after deferment (table II).

The patients in the embolic group were on average five years older when first seen than the patients in the series as a whole and the average length of follow-up was shorter (table III). They were fibrillating almost twice as commonly as patients in the other groups. The opening snap was frequently more absent and in 3 of the 6 patients in whom it was absent mitral calcification was seen on the chest X-ray or on fluoroscopy. Neither mitral incompetence nor other associated valvular lesions were commoner in the " embolic " group.

In retrospect no significant differences were found between the initial clinical features of the " static " and " progressive " cases. However it was concluded that an embolic course was more likely if a patient was over the age of 40 when first seen, was fibrillating and lacking an opening snap.

TABLE III—THE INCIDENCE OF EMBOLISM AND PROGRESSIVE BREATHLESSNESS IN RELATION TO THE NUMBER OF PATIENTS AT RISK

Years after deferment	No. at risk	Embolism	Progressive breathlessness
0–1·9	104	10	15
2–3·9	68	4	15
4–5·9	35	5	5
6–8·9	16	3	2
8–9·9	3	0	2

Relation between Atrial Fibrillation and Embolism.

Embolism occurred three times as commonly in patients who were fibrillating when first deferred by comparison with those in sinus rhythm (table IV). 5 patients formerly in sinus rhythm were found to be fibrillating for the first time after an embolic episode and so the embolus may well have been related to the onset of fibrillation. However, the occurrence of embolism was by no means confined to the onset of fibrillation; 9 patients in this series developed emboli between one and five years after the onset of fibrillation. 5 patients were in sinus rhythm before and after embolic episodes.

The Relation between Age and Embolism

The embolic incidence was five times as great in the patients aged 40 and over when first seen, by comparison with patients under the age of 40. Table V shows that this was not solely due to the increasing incidence of fibrillation in the older patients.

Results of Operation

Valvotomy was advised in 54 patients—in 39 because of progressive breathlessness on exercise and in 15 because of systemic emboli, though in 6 of these patients progressive breathlessness had also occurred, indicating " critical "

TABLE IV—RELATION BETWEEN FIBRILLATION AND EMBOLISM (EXCLUDING EMBOLISM DURING SUBACUTE BACTERIAL ENDOCARDITIS)

—	Total	In sinus rhythm throughout	Fibrillating initially	Developing fibrillation	"Presumed" fibrillation before emboli*
No. of patients	104	55	29	20	
"Embolic" ..	22 (21%)	5 (9%)	10 (34%)	7 (35%)	5
Fatal emboli ..	5 (5%)	1	3 (10%)	1	0
Emboli causing residual disability ..	9 (9%)	2	4 (14%)	3	3

* Fibrillation discovered *after* occurrence of embolus.

TABLE V—RELATION BETWEEN AGE AND EMBOLISM

—	Age (years)	Patients	Embolic
Rhythm when first seen	>40	50	18 (36%)
	<40	54	4 (7%)
Sinus rhythm	>40	35	10 (29%)
	<40	40	2 (5%)
Atrial fibrillation	>40	15	8 (53%)
	<40	14	2 (14%)

mitral stenosis (table I). For 2 patients not operated on at the Brompton Hospital full operative details were not available. 2 patients awaited operation. Thus the operative series comprised 50 patients.

The findings at operation as recorded by the surgeon confirmed that the valves in the " emboli " group were on average less severely stenosed. 7 out of 15 valve orifices were 1·25 cm. or larger, by comparison with 3 out of 35 in the " progressive " group. The surgeons amputated routinely the auricular appendage. Thrombus was more commonly recorded in the operation notes as present in the atrium in the embolic patients, though a separate prospective study has failed to show a significant difference between the incidence of clot in these two groups (Wood 1959).

In 5 patients the valve was stated by the surgeon to have been incompletely split and in 4 patients the surgeon observed that some incompetence had been produced. However, in both these groups of patients in which the valvotomy was imperfect both subjective and objective improvement occurred. So far no functional disturbance has been apparent on routine clinical examination in the patients with mild mitral incompetence.

1 patient had a right cerebral embolus at operation. 1 patient died five days after operation, probably from

TABLE VI—RESULTS OF OPERATION

—	Preoperative course		
	Total	" Embolic "	" Progressive "
No. of operations	50	15	35
Postoperative follow-up (years)	3·1	3·8	2·8
Died within 2 weeks	1	0	1
Died subsequently	2	1	1
Non-fatal emboli at operation	1	0	1
Non-fatal emboli subsequently	1	1	0

unrelieved aortic stenosis which was thought to be trivial at the time valvotomy was deferred but was found to be moderate immediately preoperatively.

Progress after Valvotomy (table VI)

50 patients were followed for an average just over three years after valvotomy, 16 of them for more than four years. At the conclusion of the study 45 of them claimed improvement in their exercise tolerance by comparison with their preoperative state.

2 patients died. The first, the patient who had a cerebral embolus at operation, died from a pulmonary embolus nine months later. The second, a patient in whom the mitral stenosis was complicated by systemic hypertension, died suddenly three months after operation and the cause of death was not discovered.

1 patient, the only one in the series to have a grossly enlarged left atrium, continued to have emboli though the appendage was removed at operation. Finally he was treated

with anticoagulants and for two years he has remained free from further emboli.

1 patient developed chronic renal disease with hypertension.

1 developed thyrotoxicosis and a retrosternal thyroid gland was excised.

In 2 patients quinidine failed to restore sinus rhythm post-operatively, and in 2 fibrillation has returned after successful conversion.

There is as yet no definite evidence of restenosis in this series, though 1 patient with moderate breathlessness on exertion has developed atrial fibrillation and the possibility cannot be excluded. In 1 patient there have been three paroxysms of fibrillation which had required hospital admission for control.

Discussion

The natural history of mitral stenosis prior to the introduction of valvotomy is well known. Grant (1933) emphasised the benign course of mitral stenosis in many patients; De Graff and Lingg (1935) pointed to the poor prognosis in cases with progressive breathlessness.

After the introduction of valvotomy some patients with critical mitral stenosis died from systemic emboli while awaiting operation. Now valvotomy tends to be advised earlier in the disease; but Turner and Fraser (1956) took the view that it was usually considered about three years too late, because the earliest symptoms of progressive breathlessness were easily overlooked. Even accepting the earliest symptoms of progressive breathlessness as an indication for valvotomy, there are many patients with signs of moderate stenosis in whom symptoms are trivial.

The present series represented a fifth of all new patients with dominant mitral stenosis seen in two cardiac clinics over a period of nine years; 354 of these new patients required valvotomy. Wood (1954), from figures quoted by Parkinson (1945), estimated that 3000 valvotomies would be required annually in this country. If the series is representative of the country as a whole, and if the same procedure of deferment is generally adopted, some 40 patients may be expected to die annually from systemic emboli while awaiting operation.

The present paper, though it suffers from the disadvantages of retrospective studies, shows that deferment of operation in patients with moderate mitral stenosis and trivial symptoms carries a high risk. If this conclusion is accepted, it would be unethical to conduct a prospective trial comparing the results of conservative treatment with those of operation in the kind of patient in whom operation is nowadays deferred.

The study throws little light on the cause of systemic embolism. Though this often occurred at the onset of uncontrolled fibrillation, it also occurred afterwards. Some patients presumably had a low cardiac output, secondary to atrial fibrillation, which may predispose to emboli before the valve size is critical (Fleming and Wood 1959). It is difficult to attribute the low incidence of embolic events following operation solely to the relief of moderate stenosis, although an improvement in the cardiac output postoperatively might be expected to reduce the likelihood of clot formation in the atrium. Excision of an enlarged atrial appendage may well have been as important as relieving the stenosis.

The alternatives which may be offered to patients with moderate mitral stenosis and trivial symptoms are (1) operation, which means appendicectomy and valvotomy, or (2) deferment, with or without anti-coagulant therapy until progressive breathlessness indicates that the stenosis is " critical ". Each patient presents an individual problem, but the risks of operation must be weighed against those of deferment.

Apart from the risk of emboli during the operation, there is a postoperative morbidity due mainly to mitral incompetence, persistent atrial fibrillation, and the post-pericardiotomy syndrome. For patients with " critical " mitral stenosis Wood (1959) has estimated that the operative mortality is less than 3% and the morbidity 10% from all causes. Against these must be balanced the embolic risk of deferring operation. The incidence of emboli in patients over the age of 40 was 36% during the follow-up period, and this finding must weigh heavily against conservative treatment, irrespective of the cardiac rhythm, for patients over that age. In younger patients who were known to be fibrillating the incidence of emboli was 14%, and so conservative treatment can hardly be recommended for such patients. For patients under the age of 40 and in sinus rhythm, the risk of systemic embolism was 5% and conservative treatment is probably justified.

The problem yet to be solved is whether immediate operation or alternatively deferment with anticoagulant therapy is preferable where the embolic risk is high. In favour of operation is the fact that embolism is rare after operation (Turner and Fraser 1956) though whether this is the result of valvotomy or removal of the atrial appendix is not known. On the other hand, early operation may lead to earlier restenosis, though with the transventricular approach a second operation is not necessarily more difficult or hazardous than the first (Belcher 1960).

Anticoagulants treatment in itself, probably carries a smaller risk than operation. But neither the extent of this nor the efficiency of anticoagulants in preventing emboli in such patients is precisely known. In addition, judging by this series, more than a third of the patients with atrial fibrillation treated with anticoagulants might be expected to require operation within three years because of progressive breathlesslness.

Summary

In 105 patients with moderate mitral stenosis and trivial symptoms operation was deferred until either a systemic embolus occurred or the patient developed progressive breathlessness on exercise. These patients were followed for an average of four and a half years after the decision to defer valvotomy.

Systemic embolism occurred in 22 of the patients, causing 5 deaths, excluding 1 death during subacute bacterial endocarditis.

More than half the patients over the age of 40 who were fibrillating when first seen had systemic emboli before operation was advised.

The high incidence of embolism shows that the present custom of deferring operation in patients with moderate stenosis and trivial symptoms is unsatisfactory. In young patients still in sinus rhythm deferment is probably justified, but the present results suggest that in the remainder of this group operation should be considered before progressive breathlessness on exertion occurs. Alternatively anticoagulant therapy might be given until progressive breathlessness is evident, but there is as yet no report on its efficacy in such patients.

My thanks are due to Dr. Paul Wood and Dr. R. V. Gibson for permission to study patients under their care and to the surgeons who performed the operations. I am grateful to Dr. Wood for his encouragement and helpful criticism.

References at foot of next column

LEVEL OF HÆMOGLOBIN IN WHOLE BLOOD AND RED BLOOD-CELLS, AND PROPOSED CONVENTION FOR DEFINING NORMALITY *

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IN studying physiological variables, the conventional procedure is to compare patients with normal individuals. The normal values are usually determined from a small series of selected subjects, the criteria for normality being subjective, arbitrary, and undefined.

Extrapolation from a small sample to the parent population is valid, provided the sample is randomly selected and the measured variable is normally distributed in the parent population (Yule and Kendall 1950). If the sample is not randomly selected and the distribution in the parent population is much skewed or leptokurtic, extrapolation is likely to be misleading (see fig. 1).

Many measured variables do depart greatly from normal, even in series selected as normal.

Thus skewed distributions have been described for body-weight (British Association 1883), arterial blood-pressure (Hamilton et al. 1954), cerebrospinal-fluid pressure (Merritt and Fremont Smith 1937), duration of menstruation (Fluhmann 1939), mean red-blood-cell diameter (Price Jones 1933), blood clotting-time and retraction-time (Tocantins 1946), prothrombin-time (Nygaard 1941), bleeding-time (O'Brien 1951), eosinophil-count (Muehrcke et al. 1952), serum group A and B agglutinin titres (Wiener 1943), gastric acidity (Lerman et al. 1932), salivary pH (Brawly 1939), postabsorptive blood-sugar (Lozner et al. 1941), whole-blood riboflavine (Prager et al. 1958), plasma-pepsinogen (Hirschowitz 1955), plasma and red-cell cholinesterase (Rider et al. 1957), whole-blood ammonia (Calkins 1956), urine-coproporphyrin output (Zieve et al. 1953), and serum cholesterol, acid and alkaline phosphatase, bilirubin, creatinine, urea, amylase, potassium, and total globulin (King and Wootton 1953).

Some of these distortions could result from the observed variable being a derivative function of a more fundamental variable which is itself normally distributed, but the majority cannot be so explained. In many of the above instances, the arithmetic mean and standard deviation are quite unrepresentative of the modal value and the scatter around the mode. A convention for circumventing this difficulty was devised during a survey of red-cell composition in disease.

Proposed Convention

The modal value is taken as the point of reference. A gaussian curve is superimposed on the mode, and this range is defined as the arbitrary normal. This statistic simply describes the bulk of the observed population, and does not connote optimum or ideal. The convention is applicable to routine laboratory data, without selecting normals. A frequency distribution is drawn up for 100–200 consecutive values, to discover whether the curve is roughly symmetrical.

Equal Divergence from Normal

The mean and mode will coincide, but abnormal values at the tails will exaggerate the variance. In the gaussian curve, 68% of the population fall within one standard deviation from the mean. We calculate the number equal to 34% of our total population, interpolate their distance from the mean value, and take the mean of the two deviations so obtained; we then have an approximate estimate of the standard deviation (S.D.) which is independent of the distribution at the tails of the curve. If this approximate estimate or interpolated S.D. is less than the S.D. calculated by the orthodox root mean square procedure, we may suppose that it is a better estimate of the variance for the normal population than the calculated value for the crude population.

For example, in the present survey 102 males had a mean value for mean corpuscular hæmoglobin concentration (M.C.H.C.) of 31·8 g., and a median value of 31·87%, with a calculated S.D. of ±1·8%. Ignoring the moderate degree of skewing and treating the distribution as symmetrical, 34% of the population equals 35 to the nearest whole number. Since there are 51 observations in each half, the limit for one S.D. should coincide with the 51st minus 35th—i.e., the 16th—value from the end on each side. Interpolating the 16th value on the grouped frequency data gave values of 30·46 and 33·31 respectively. Half the difference between these two yields a figure of ±1·42 as the interpolated deviation about the mean. The calculated S.D. was ±1·8, so the 95% range for the M.C.H.C. in one case would be 29% greater than in the other.

The orthodox procedure for correcting this type of abnormal distribution is the application of Chauvenet's criterion, but this involves a great deal more calculation than the present simple convention.

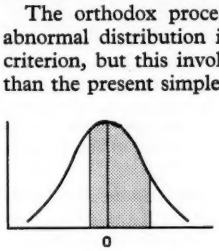

Fig. 1.

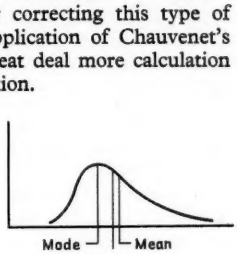

Fig. 2.

Fig. 1—This illustrates a possible error in selecting "ideal" normals. The mean and variation of the selected sample may not be representative of the true population.

Fig. 2—In a skewed distribution, the mean and median are moved farther from the centre than the mode.

Unequal Divergence from Normal

If the abnormals in the mixed population diverge more in one direction than the other, the distribution is said to be skewed. This situation often arises—for instance, anæmia is much commoner than erythrocytosis, high blood-ureas are much commoner in diseased states than low values. One way of handling the data is to scale down the difference by using the logarithms of the observed values instead of the actual values; but this involves considerable calculation, the results are not always easy to interpret, and occasionally this procedure tends to skew the data in the opposite direction. The problem is to get an approximate estimate of the arithmetical mean and variance for the normal population, from the crude data on the mixed population. When a distribution is skewed by adding observations to one end, all the indices

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Belcher, J. R. (1960) *Lancet*, i, 181.
De Graff, A. C., Lingg, C. (1935) *Amer. Heart J.* **10**, 459, 478, 630.
Fleming, H. A., Wood, P. H. (1959) *Brit. Heart J.* **21**, 117.
Grant, R. T., (1933) *Heart*, **6**, 275.
Parkinson, J. (1945) *Lancet*, ii, 657.
Turner, R. W. D., Fraser, H. R. L. (1956) *ibid.* ii, 525.
Wells, B. (1954) *Brit. Heart J.* **16**, 261.
Wood, P. H. (1954) *Brit. med. J.* i, 1051.
— (1959) Personal communication.

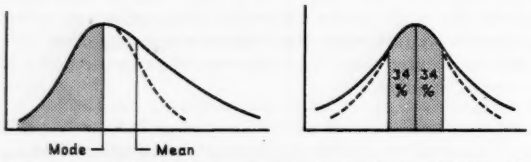

Fig. 3—If the distribution is skewed, the mode is calculated, the deviation on the normal side of the mode is calculated, and this value is interpolated on the other side. If the distribution is symmetrical but kurtotic, the population volume corresponding to one S.D. is interpolated from the mean.

of population density are shifted, but the mode is moved less than the mean or the median (fig. 2) (Moroney 1953). The mode is not susceptible to precise calculation; but, for moderate degrees of skewness, mean−mode=3 (mean −median) (Tippett 1941). In laboratory practice most of the data fall in the normal range; since skewing is therefore moderate, this formula can be employed and the mode calculated precisely. This will give the best estimate of the mean for the normal population. As we are postulating a gaussian distribution, the population around the mode should be symmetrical. Accordingly the standard deviation is calculated as usual, but only figures on the supposedly normal side of the mode are used (fig. 3). Since the S.D. is expressed as ±, the number of observations in testing for significance is twice the number actually employed in making the calculation.

For example, in the present study the mean Hb of 102 males was 13·7 g. per 100 ml., with a median value of 13·92 g. and a calculated mode of 14·36 g. The S.D. was ±2·2 g. per 100 ml., and the interpolated deviation about the mode was 1·34 g. per 100 ml. When these figures were diluted with the observations on the 126 females, the mean fell to 13·0 g., and the S.D. was increased slightly to 2·3 g. However, the median value for the combined data was 13·46 g., and the calculated mode was 14·38 g. with an interpolated deviation about the mode of 1·32 g. per 100 ml. Thus there was no shift in the mode or the interpolated variance although there was a notable fall in the mean and a slight increase in the variance of the crude data.

It is not suggested that these conventions for interpolating the normal mean and range from the crude data represent anything more than an approximate estimation for the whole population. It seems probable that they will provide a better guide to the population than the operational method discussed above, which is based on dubious premises, and often involves small samples from a population dissimilar in respect to age, occupation, and social and nutritional status, to those studied by the clinician. The evidence that the proposed conventions have empirical value is presented in the next section.

Methods and Materials

This laboratory serves a general hospital with a hundred fever beds, and supplies a general-practitioner service. Unselected venous-blood samples presented for routine analysis were used. The observations were made between July, 1958, and January, 1959. Most of the blood samples were drawn in the mornings. Only children under 14 years of age have been excluded from the data. There were 102 adult males (mean age 47·6±18 years) and 126 adult females (mean age 46·4 ±18 years). In addition to the estimations listed below, the samples were analysed for total protein, iron, and water in the red cells.

Hæmoglobin

The cyanmethæmoglobin method was employed (King and Wootton 1956). The diluting reagent was slightly modified, containing 2·0 g. sodium bicarbonate, 0·6 g. potassium ferricyanide, and 0·2 g. sodium cyanide in 1 litre of distilled water. The method was standardised by periodical estimates of the iron content of blood-cells, using the factor of 338 mg. of iron to 100 g. Hb. It was established, by measuring 400 specimens, that the cyanmethæmoglobin method gives slightly higher values than the oxyhæmoglobin method, the average difference being 0·2 g. per 100 ml. The coefficient of variation of the method was ±0·7%, established by measuring the same sample twenty times over the period of a week.

Mean Corpuscular Hæmoglobin Concentration (M.C.H.C.)

This was measured directly. The cells were packed by centrifuging at 4000 *g* for 30 minutes, and the plasma was removed by suction; 0·02 ml. of mixed cells were then analysed as for whole-blood hæmoglobin. The coefficient of variation was ±1·96% of the mean value.

Packed-cell Volume

This was determined directly and indirectly.

Direct determination.—Initially this was performed as specified by Wintrobe (1946). Later it was discovered that this procedure did not always give maximum packing, and thereafter 5000 r.p.m. for 30 minutes was employed. The coefficient of variation was ±1·39% of the observed value.

Indirect estimation was calculated from the formula:

$$\frac{\text{Whole-blood Hb}}{\text{Red-cell Hb}} \times 100.$$

The coefficient of variation was ±1·96%. The indirect method gave very similar results to the direct method, once maximum packing was attained in the latter procedure.

The results described below were based on the indirect method, since this was more relevant to the chemical analyses of the red cells performed at the same time.

Results

The statistical results are summarised in table I.

The figures shown in table I were compared with corresponding reported data. The latter were selected on the following criteria: (*a*) minimum selection of subjects; (*b*) largest available series; (*c*) reliable methods, with special reference to photoelectric colorimetry, and standardisation of hæmoglobin estimations by analysing iron content of the pigment.

Hæmoglobin

The main series found are listed in table II. The largest published series is that in the Medical Research Council (1945) survey. In the M.R.C. survey, unlike the others cited, visual colorimetry was used instead of photoelectric methods. The errors involved in the visual method were discussed by R. G. Macfarlane in an appendix to the M.R.C. report. The S.D. listed here has been corrected for the observed experimental error to give a

TABLE I—SUMMARISED STATISTICAL DATA FOR PRESENT SURVEY

—	102 males				126 females			
	Age (yr.)	Hb (g. per 100 ml.)	M.C.H.C. (%)	P.C.V. (%)	Age (yr.)	Hb (g. per 100 ml.)	M.C.H.C. (%)	P.C.V. (%)
Mean	47·6	13·7	31·8	42·4	46·4	12·5	31·2	40·0
S.D.	15·4	2·2	1·8	6·3	18·6	2·2	1·45	6·6
Calculated mode	..	14·4	32·0	45·1	..	13·3	32·0	42·2
Interpolated deviation from mean or mode	..	1·34	1·4	4·1	..	1·34	1·3	4·0

TABLE II—COLLECTED DATA ON NORMAL HÆMOGLOBIN LEVELS (G. PER 100 ML.)

Source and place	No.	Values		Standard deviation	
		Males	Females	Males	Females
M.R.C. 1945 (U.K. 1943) ..	4561	14·9	..	1·11	..
	7787	..	13·7	..	1·37
Davidson et al. 1936 (Aberdeen)	93	14·2	..	..	..
	90	..	13·1	..	..
Marshall 1946 (Scotland) ..	102	14·7	..	..	..
	269	..	13·6	..	..
Present series (Birmingham 1959)	84	14·4	..	1·34	..
	94	..	13·3	..	1·34
Young et al. 1953 (London) ..	73	..	13·1	..	1·20
Milam and Muench 1946 (U.S.A.)	611	14·4	..	1·21	..
	838	..	13·1	..	1·25
Hawkins et al. 1954 (Canada) ..	798	14·4	..	1·34	..
	875	..	13·1	..	1·14
Pett and Ogilvie 1948 (Canada)	321	14·6	..	..	..
	329	..	12·8	..	..
Judy and Price 1958 (U.S.A.) ..	84	..	12·8	..	1·15
Semmence 1959 (Yorkshire) ..	97	14·3	..	1·05	..
	154	..	13·6	..	1·05
Snell 1950 (Japan)	259	14·1	..	1·16	..
Ohlson et al. 1944 (U.S.A.) ..	4550	..	12·6	..	1·11
			13·4	..	..
Standard textbooks:					
Whitby and Britton 1953 ..	..	15·6 (14–17)	..	..	..
	..	..	13·7 (12–15·5)	..	..
Dacie 1950	..	13·5–18·0	..	..	..
	..	..	11·5–16·4	..	..
Wintrobe 1946	..	16·0 (14–18)	..	..	..
	..	..	14·0 (12–16)	..	..
Sandoz 1952	..	..	14·5–20·0	..	..

best estimate of the intrinsic S.D. Where the workers cited used the oxyhæmoglobin method, their values have been corrected by adding 0·2 g. per 100 ml. to make their values comparable to those with the cyanmethænoglobin method. The figures have been recalculated in many instances to give comparable age-groups, and to conform to the factor of 338 mg. of iron per 100 g. Hb. Sources of variation in blood-hæmoglobin levels will not be discussed here. Hawkins et al. (1954) have demonstrated the effect of age, and Sundermann et al. (1953) have discussed many of the other variables. It may be noted, however, that several workers have demonstrated a pronounced seasonal variation in levels, the maximum difference being of the order of 10% of the highest value (Engle-breth-Holm and Videbæk 1948, Coulthard 1958). The subjects of the M.R.C. series were volunteers and were younger than many of the other series cited, the mean age for males being 38 years, and for females 33.

Table II demonstrates two points: (1) the present method of analysis gives results comparable to the other original series; and (2) the textbook means and ranges are considerably higher than any of the values in the more recent reports.

TABLE III—COLLECTED DATA ON NORMAL HÆMATOCRIT VALUES (%)

Source and place	No.	Values		Standard deviation	
		Males	Females	Males	Females
Snell 1950 (Japan)	234	44·7	..	3·4	..
	278	..	40·5	..	3·16
Vallee et al. 1949 (U.S.A.) ..	14	45·8	..	3·03	..
	14	..	42·4	..	2·8
Present series (Birmingham 1959)	68	45·1	..	4·13	..
	70	..	42·2	..	4·02
Standard textbooks:					
Whitby and Britton 1953 ..	..	45 (42–47)		..	..
Dacie 1950	..	40–54	36–47	..	..
Wintrobe 1946	..	47·0	..	4·7	..
	..	..	42·0	..	3·3
Sandoz 1952	..	39–52	35–48	..	..

Hæmatocrit

There are virtually no reported random series with which to compare the present results, apart from that of Snell (1950). Vallee et al. (1949) published a small series of selected "normals" which are included for comparison. These results are listed in table III. It can be seen that in this case, the reported figures and those from the textbooks are in better agreement, though the reported lower limits are outside the normal ranges cited in the textbooks.

Mean Corpuscular Hæmoglobin Concentration

Snell's (1950) study appears to be the only randomly selected series that has been reported in recent years. The other figures listed have all been compiled from special groups, or from samples selected for "normality". The data are listed in table IV. This table shows that the mean figure cited in the original surveys is on or below the lower limit of normal accepted by the text-books. Since this is one of the most useful laboratory investigations, for diagnosing iron deficiency on the one hand, or for revealing cellular dehydration on the other, these discrepancies are unfortunate.

Comment

These tables show that the proposed convention for analysing laboratory data gives results which are usefully comparable with those reported elsewhere. They also show that the more recently reported figures for these variables do not agree well with those cited in the standard textbooks. The most likely reason for this is that the

TABLE IV—COLLECTED DATA ON NORMAL M.C.H.C. LEVELS (%)

Source and place	No.	Value		Standard deviation	
		Males	Females	Males	Females
Snell 1950 (Japan)	216	32·0	..	1·51	..
	214	..	31·8	..	1·36
MacGeorge 1936 (London) ..	50	33·0	..	30·7–35·1	..
Sturgeon 1959 (U.S.A.)	31	33·0	..	1·4	..
	20	..	31·0	..	0·8
Vallee et al. 1949 (U.S.A.) ..	14	32·2	..	1·6	..
	14	..	30·8	..	3·1
Present series (Birmingham 1959)	102	32·0	..	1·42	..
	102	..	32·0	..	1·36
Standard textbooks:					
Whitby and Britton 1953 ..	..	33 (32–38)			
Dacie 1950	..	32–36			
Wintrobe 1946	..	34		1·3	
Sandoz 1952	..	33–37			

textbook figures are based on selected "ideal normals", which therefore prejudge the question they purport to answer—namely, what is the normal level. The primary data cited here, on the other hand, have been established mainly on random samples.

REFERENCES

Brawly, R. E. (1939) *J. dent. Res.* **18**, 431.
British Association (1883) Report of Anthropometric Committee; p. 256.
Calkins, W. G. (1956) *J. Lab. clin. Med.* **47**, 343.
Coulthard, A. J. (1958) *Clin. Chim. acta*, **3**, 226.
Dacie, J. V. (1950) Practical Hæmatology. London.
Davidson, L. S. P., Fullerton, H. W., Campbell, R. M. (1936) *Brit. med. J.* ii, 195.
Englebreth-Holm, J., Videbæk, A. (1948) *Blood*, **3**, 612.
Fluhmann, C. F. (1939) Menstrual Disorders. Philadelphia.
Hamilton, M., Pickering, G. W., Fraser Roberts, J. A., Sowry, G. S. C. (1954) *Clin. Sci.* **13**, 11.
Hawkins, W. W., Speck, E., Leonard, V. G. (1954) *Blood*, **9**, 999.
Hirschowitz, B. I. (1955) *J. Lab. clin. Med.* **46**, 568.
Judy, H. E., Price, N. B. (1958) *J. Amer. med. Ass.* **167**, 563.
King, E. J., Wootton, I. D. P. (1953) *Lancet*, i, 470.
— — (1956) Microanalysis in Medical Biochemistry. London.
Lerman, J., Pierce, F. D., Brogan, A. J. (1932) *J. clin. Invest.* **11**, 155.
Lozner, E. L., Winkler, A. W., Taylor, F. M. L., Peters, J. P. (1941) *ibid.* **20**, 507.
MacGeorge, M. (1936) *J. Path. Bact.* **42**, 67.
Marshall, A. J. (1946) *Glasg. med. J.* **27**, 1.

References continued overleaf

TREATMENT OF PAIN IN PREAXIAL BORDER OF UPPER LIMB

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PAIN in the fifth, sixth, and seventh cervical dermatomes (i.e., the preaxial border of the upper limb) is common and often disabling. We have found that treatment by short-wave diathermy and neck traction in the neutral or extended position not only is valueless but also aggravates the pain considerably. We have obtained complete relief of symptoms in almost all our patients by neck traction in *flexion* with various degrees of rotation of the neck towards the painful side.

Clinical Picture

In an analysis of a hundred consecutive patients we found that:

1. The average age of the patients was 47 years, the youngest being 33 and the oldest 63; the proportion of men to women was 2 to 1.

2. In 90% of our patients the onset of the pain was insidious, and in the remaining 10% it followed either a violent twist of the neck or a pull on the arm.

3. Although all our patients admitted to discomfort within the total area of the preaxial border of the limb, 60% complained predominantly of pain in the preaxial border of the upper arm (c5) and 40% of pain in the preaxial border of the forearm and first three digits (c6 and c7).

4. The pain was described as aching, and if in the forearm and the digits was always associated with paræsthesiæ and subjective numbness.

5. None of our patients showed any muscle wasting, alteration in the normal reflex responses, or objective sensory loss.

6. Patients complaining predominantly of c5 pain had an acutely tender area at the insertion of the deltoid, and patients complaining predominantly of c6 pain had an acutely tender area overlying the posterior interosseus nerve as it emerges from beneath the supinator and crosses the shaft of the radius. Although many patients had tenderness in both areas, the deltoid and radial tenderness was always present in the predominantly c5 and c6 pains.

7. X-ray examination in anteroposterior, lateral, and both oblique views of the cervical spine revealed no significant changes, the general picture being that of degenerative changes corresponding with those normally found in succeeding age-groups.

Technique of Treatment

With the patient supine the following observations are made: (1) the range and any painful limitation of neck movements; (2) the subjective sites of pain, tenderness, and paræsthesiæ; (3) the range and painful limitations of shoulder movements (see below).

The head is supported on three or four pillows with a small electric pad behind the neck and upper thoracic region to aid relaxation. The halter (Niels Larsen type) is applied and connected to a 22-in. spreader. The face is turned towards the painful arm. The pulley circuit is then attached with a weight of 14 lb. at the other end (fig. 1). A few patients may require up to 20 lb.

Fig. 1—The "comfortable" position in traction.

Treatment for the Neck

If there are painful limitations of neck movements these should be treated along orthodox lines before traction in flexion is started.

Angle of Pull

There are two variables here: (1) the degree of neck flexion; (2) the amount of rotation.

The amount of cervical flexion and rotation at which traction is applied must be determined by experiment. We have found that the more proximal the pain, the greater the amount of flexion required—in some cases being so great that the ascending and descending pulley ropes lie parallel (fig. 2). As the patient's symptoms regress, less rotation is required.

The patient signifies with the "thumbs-up" sign when the pain recedes, which it usually does about half a minute after the correct angle of traction has been found (fig. 3). We use a pulley hung from a fixed overhead bar and vary the direction of pull by moving the couch (figs. 2 and 4).

Manual traction.—This is equally effective but takes up more time; it is, of course, ideal for the patient being treated at home.

Home Management

86% of our patients complained of pain either at night or on waking, suggesting that their sleeping posture was a contributory cause. We instruct our patients to sleep with two pillows in one pillowcase, and never to sleep prone with head turned sideways on the pillow. They must lie either on their sides or back. A sponge rubber collar (Stamm collar) is invaluable in severe cases.

DR. PRYCE: REFERENCES—*continued*

Medical Research Council (1945) *Spec. Rep. Ser. med. Res. Coun., Lond.* no. 252.
Merritt, M. H., Fremont Smith, F. (1937) Cerebrospinal Fluid. Philadelphia.
Milan, M. F., Muench, H. (1946) *J. Lab. clin. Med.* **31**, 878.
Moroney, M. J. (1953) Facts from Figures; p. 48. London.
Muehrcke, R. C., Eckert, E. L., Kark, R. M. (1952) *J. Lab. clin. Med.* **40**, 161.
Nygaard, K. K. (1941) Hæmorrhagic Diseases. St. Louis.
O'Brien, J. R. (1951) *J. clin. Path.* **4**, 272.
Ohlson, M. A., Cederquist, D., Donelson, E. G., Leverton, R. M., Lewis, G. K., Himwich, W. A., Reynolds, M. S. (1944) *Amer. J. Physiol.* **142**, 727.
Pett, L. B., Ogilvie, C. F. (1948) *Canad. med. Ass. J.* **58**, 352.
Prager, M. D., Hill, J. H., Speer, R. J., Goerner, M. (1958) *J. Lab. clin. Med.* **40**, 161.
Price Jones, C. (1933) Red Blood Cell Diameters. London.
Rider, J. A., Hodges, J. L., Swader, J., Wiggins, A. D. (1957) *J. Lab. clin. Med.* **50**, 376.
Sandoz (1952) Atlas of Hæmatology. Sandoz, Ltd., Basle.
Semmence, A. (1959) *Brit. med. J.* ii, 1153.
Snell, F. M. (1950) *Blood*, **5**, 89.
Sturgeon, P. (1959) *Brit. J. Hæmat.* **5**, 31.
Sunderman, F. W., MacFate, R. P., MacFadyen, D. A., Stevenson, G. F., Copeland, B. E. (1953) *Amer. J. clin. Path.* **23**, 519.
Tippett, L. H. C. (1941) The Methods of Statistics; p. 29. London.
Tocantins, L. M. (1946) *Med. Clin. N. Amer.* **30**, 1361.
Vallee, B. I., Lewis, H. D., Altschule, M.D., Gibson, J. G. (1949) *Blood*, **4**, 467.
Whitby, L. E. H., Britton, C. J. C. (1953) Disorders of the Blood. London.
Wiener, A. S. (1943) Blood Groups and Transfusion. Springfield, Ill.
Wintrobe, M. M. (1946) Clinical Hæmatology. London.
Young, J., King, E. J., Wood, E., Wootton, I. D. P. (1953) *J. Obstet. Gynæc. Brit. Emp.* **53**, 251.
Yule, G. U., Kendall, M. G. (1950) An Introduction to the Theory of Statistics. London.
Zieve, L., Hill, E., Schwartz, S., Watson, C. J. (1953) *J. Lab. clin. Med.* **41**, 663.

Fig. 2—Full flexion.

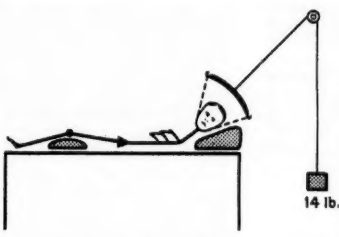

Fig. 4—Moderate flexion.

The following simple manœuvre by the patient is very useful once recovery is started:

The patient sits comfortably; he then relaxes forward from his *upper thoracic* region with his neck fully relaxed until his chin touches his chest. This produces a strong stretching feeling in the lower neck. He then rotates his face towards the affected side, and allows his head to fall once more into the midline. This will in many instances remove pain, and is useful for the patient who, though nearly cured, gets an occasional " twinge ".

Results

Of the 100 patients treated in this way 90 obtained complete relief within about half a minute of the application of traction. Once this was discontinued the relief that they had obtained lasted for from a few minutes to a few hours. In the succeeding days of treatment the duration of relief gradually increased until each patient became free of pain. The average number of treatments was eighteen, the least being five (in a patient aged 38 years) and the greatest being forty-five (in a patient aged 61). Throughout the whole series we found that in general the younger the patients the more rapidly they became pain-free.

Of the remaining 10 patients, 6 did not obtain any relief until the third day of treatment. This illustrates the great difficulty that is sometimes encountered in finding the exact direction of pull required in order to relieve pain. When the correct direction was found all 6 were subsequently relieved completely of their symptoms.

Fig. 3—Relief of pain by manual traction.

4 patients, all in their late 50s, obtained complete relief of their symptoms during traction, but once this was discontinued their symptoms returned immediately. No amount of traction resulted in even the slightest period of relief for these patients once the traction was taken down. All 4 were subjected to a manipulation under anæsthesia. 2 obtained immediate full relief; the other 2 greatly improved, obtaining full relief after a further three weeks' intermittent traction.

Of the 100 patients, 3 had a recurrence within two months and 3 within six months. All of them were relieved by a further course of traction in flexion.

Relation to Painful Limitation of Shoulder Movement

In the examination and treatment of this series of patients, we were surprised to discover that in 30 out of the 60 patients complaining of upper-arm pain (C5) there was also painful limitation of either external or internal rotation at the shoulder-joint (fig. 5). We were further surprised to find that in the younger patients a full painless range, or greatly increased range, of movement was obtained at the shoulder-joint when the pain had gone out of the arm, in traction in flexion (fig. 6). In the older patients with longstanding symptoms, although the painless range of movement was increased during cervical traction in flexion, a full range was not always obtained, and this we ascribed to an associated adhesive capsulitis. Nonetheless, the application of cervical traction in flexion was a most useful adjunct in the mobilisation of the shoulder in these patients, and also served to subtract the amount of apparent limitation of movement due to muscle spasm from the true stiffening.

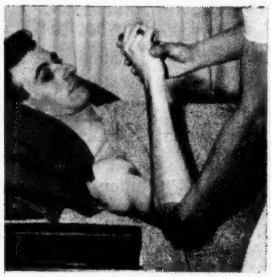

Fig. 5.

Fig. 6.

Fig. 5—Almost complete limitation of external rotation.

Fig. 6—Restitution of full external rotation as soon as pain has been relieved by cervical traction.

Comment

When dealing with a purely empirical method of treatment such as this, it is always a great temptation to conjecture why the pain is relieved. Rather than dogmatise we prefer merely to remark on the following points:

1. The neurocentral joints of Luschka form the ventromedial border of the intervertebral foramina of the lower cervical spine, and lie in intimate contact with the issuing spinal nerves. In the 40s and 50s these joints often become subject to hypertrophic degenerative changes, which later become evident in radiographs. The issuing spinal nerve bends around the neurocentral joint, and an excrescence from here must increase the angulation of the nerve at this point. Supposedly this would predispose to friction on cervical or brachial movements with consequent pain and paræsthesiæ.

2. Degeneration occurs most often at the C4–5 and C5–6 neurocentral joints—that is to say, those joints which lie in intimate contact with the 5th and 6th cervical nerves.

3. The most common sites of pain in the arm are in the 5th and 6th cervical dermatomes.

4. All the muscles contributing to the rotator mechanism of the shoulder-joint are supplied by the 5th and 6th cervical nerves.

Our thanks are due to the physicians and surgeons of St. Bartholomew's Hospital for permission to treat their patients; to Mr. H. Jackson Burrows for his many helpful criticisms; to Mr. N. K. Harrison and the department of medical photography, St. Bartholomew's Hospital; and finally to the staff of the physiotherapy department for their cooperation.

TREATMENT OF SEVERE ACUTE BARBITURATE POISONING BY FORCED DIURESIS AND ALKALINISATION OF THE URINE

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THE prognosis of acute barbiturate poisoning has improved considerably in the last decade (Clemmesen 1959), primarily because of the general use of adequate ventilation and supportive treatment in the form of blood or plasma infusions. But other things being equal, increasing the rate of excretion of barbiturate from the body will improve the prognosis. This report shows how forced diuresis and alkalinisation of the urine increases the barbiturate excretion in patients with severe acute poisoning. It confirms the favourable results obtained by Ohlsson (1949) and by Mollaret et al. (1959), who first used these therapeutic principles clinically.

The Regime

The details of treatment have evolved gradually, and the following description refers to the scheme used in the last nine cases.

Urea was the diuretic agent, given in 15% solution in the isotonic standard fluid described below. During the first 3–4 hours 200 ml. of this urea solution was given hourly. These first hours should be regarded as a priming period during which the blood-urea level is brought up to about 250 mg. per 100 ml. Afterwards a continuous infusion of urea was given at a fairly constant rate. The amount varied according to the patient's renal function and body-weight. In most cases 100 ml. of the 15% urea solution was given hourly. Minor adjustments of the urea load were necesary to keep the diuresis at 500–800 ml. per hour.

As the diuresis increased, additional fluid without urea was given intravenously, the hourly intravenous volume being adjusted to equal the diuresis of the previous hour. The additional fluid was composed of potassium chloride 12 mEq. per litre, sodium lactate 40 mEq. per litre, and glucose 200 mEq. per litre. In the last three cases 4–20 insulin i.u. per litre were added over several hours.

This scheme makes no allowance for the degree of hydration before treatment, nor for non-renal water loss or water liberated from the metabolic breakdown of tissue and other combustible compounds. A moderately negative water balance was often suggested clinically when patients had been unconscious for some hours before admittance to hospital. A litre of isotonic sodium bicarbonate was usually given subcutaneously to cover the supposed deficit and to make the urine alkaline quickly. In addition isotonic fluid was given subcutaneously as judged necessary. In most cases the treatment was discontinued when the patient was able to answer "yes" or "no". 2 litres of isotonic standard fluid without urea were then given subcutaneously over 3 hours. Additional parenteral fluid was given intravenously, when the need arose, but most patients were able to take fluid by mouth according to their thirst. The urea-induced polyuria rapidly subsided in all cases.

Methods

The hourly urinary volume was measured, and the pH was determined using indicator paper. In the last three patients the urine was also tested hourly for glucose by the semi-quantitative testape method. The urine was pooled for 8-hour periods and analysed for sodium, potassium, chloride, hydrogen ion, and creatinine by conventional methods, and for barbiturate by the spectrophotometric method of Lous (1954b). Venous blood was collected at the mid-point of each 8-hour period for barbiturate determination (Lous 1950, 1954a). The daily venous-blood analyses included routine laboratory tests of hæmoglobin and protein content, and of plasma sodium, potassium, calcium and phosphate (in the last five patients only), chloride, total CO_2, urea, and creatinine. Arterial blood was analysed in most cases for oxygen saturation, pH, and pCO_2, as well as for standard bicarbonate (i.e., the bicarbonate in plasma standardised for respiratory effects by equilibration at a pCO_2 of 40 mm. Hg). The excretion and renal clearance of barbiturate were calculated for the various 8-hour periods. (Some barbiturates are only partially ultrafiltrable in the plasma [Lous 1959b]; therefore, for such compounds this clearance is smaller than that calculated on the basis of ultrafiltrable barbiturate.) The barbiturates were identified by paper chromatography of serum, as described by Wright (1954).

The Patients

Fourteen patients with severe acute barbiturate intoxication were studied. They were aged 23–73 years (table I).

All except case 9 were in profound coma when treatment was started. Case 9 was a chronic addict, and she regained consciousness at a very high serum-barbiturate level; afterwards the treatment was continued by mouth. Several patients received manual intermittent positive-pressure assistance of respiration, and one (case 12) was treated with a mechanical

TABLE I—CLINICAL DATA IN 14 CASES OF SEVERE ACUTE BARBITURATE INTOXICATION TREATED BY UREA-INDUCED FORCED DIURESIS AND ALKALINISATION OF THE URINE

Case no.	Age (yr.)	Sex	Barbiturate: Compound	Barbiturate: Dose (g.)	Barbiturate: Concentration (mg. per 100 ml.)	Creatinine-clearance (ml. per min.)	Length of coma (hr.)	Length of treatment (hr.)	Complications	Diuresis: Total (l.)	Diuresis: Rate (ml. per min.)	Barbiturate excretion: U/P ratio	Barbiturate excretion: Clearance (ml. per min.)	Total barbiturate excreted (g.)	Average elimination-rate (% per 24 hr.)
1	43	F	Phenylethyl	5	16·8	130	44	24	..	7·2	5·0	1·3	6·5	1·4	23
2	23	F	Phenylethyl	?	26·3	130	106	24	..	8·5	5·9	1·2	7·1	1·7	24
3	32	M	Allylisopropyl+diethyl	18	23·0*	120	48	24	..	13·1	9·1	3·0	27·3	4·2*	58
4	70	F	Diethyl	12	32·4	30	115	48	..	13·3	4·6	2·5	11·5	5·0	42
5	61	F	Allylisopropyl	10	12·9	90	95	33	..	11·5	5·8	2·0	11·6	0·9	62
6	55	M	Phenylethyl	7	16·8	130	73	59	..	23·1	6·5	1·3	8·5	4·0	25
7	35	F	Diethyl	?	17·7	120	41	13	..	6·8	8·7	2·7	23·5	2·4	51
8	73	F	Diallyl	?	11·7	40	62	42	+†	13·2	5·2	1·3	6·8	1·0	34
9	36	F	Phenylethyl	7	16·6	120	7	40	..	17·2	7·2	0·9	6·5	1·7	39
10	43	F	Allylisopropyl	17	10·5	40	92	92	..	46·7	8·5	1·6	13·6	5·0	58
11	44	F	Allylisopropyl+diethyl	?	11·5*	100	35	26	..	15·5	9·9	1·9	18·8	2·5*	42
12	67	F	Ethylallyl	?	35·4	90	64	76	+	40·8	9·0	1·8	16·2	9·6	61
13	26	F	Phenylethyl	5	14·5	160	62	38	..	20·3	10·6	1·2	12·7	2·5	36
14	58	F	Allylisopropyl+diethyl	?	19·1*	80	78	43	..	30·8	11·9	1·5	17·9	4·9*	54

* As the diethyl compound. † Died from pulmonary embolism.

respirator. They were all given blood and plasma infusions, and noradrenaline was added in several cases to establish and maintain a satisfactory circulatory state. The patients were selected solely on the basis of high serum-barbiturate values from five hundred and thirty cases of acute poisoning admitted during 7 months to the intoxication centre of Copenhagen, in the psychiatric department of Bispebjerg Hospital. This centre receives about half of all the patients with acute intoxication in Copenhagen, only the severest cases being admitted.

All fourteen cases were treated with forced diuresis and alkalinisation of the urine when the plasma-barbiturate level was steadily decreasing; hence the elimination of the drug could be estimated. Three additional patients with phenylethyl-barbituric-acid poisoning were treated. Two of these died from extensive bronchopneumonia before a steadily falling plasma level was established. The third patient, a chronic addict, regained consciousness shortly after diuretic therapy was started and it was therefore discontinued within a few hours.

The period of unconsciousness in these patients varied between 7 and 115 hours. An estimate of the amount of barbiturate ingested was available in some cases. The doses were of 5–18 g. and five different barbiturates were involved—namely, diethyl, diallyl, phenylethyl, allylethyl, and allylisopropyl barbituric acid. In eleven patients only one compound was found on paper chromatography, whereas three had taken a combination drug containing equal parts of allylisopropyl and diethyl barbituric acid.

Treatment with the alkaline urea solution lasted from 13 to 92 hours (average 42 hours). Only moderate alkalosis of arterial blood was found during treatment (arterial pH 7·39–7·54). The highest serum-urea levels were between 213 and 478 mg. per 100 ml. The diuretic response was 4·6–11·9 ml. per min., averaging 7·7 (i.e., about 11 litres per 24 hours).

Thirteen patients recovered, and the one who died (case 8) had a large pulmonary embolus at necropsy.

Effects of Treatment

With the fluid mixture used in the last nine cases (see above) certain tendencies were noted in the plasma-electrolytes. The potassium level was slightly subnormal, and the sodium normal or slightly subnormal; this was readily corrected by giving additional electrolytes. Serum-calcium was determined in the last five patients, and subnormal values of 8–9 mg. per 100 ml. were found. The problem of hypocalcæmia in mild alkalosis deserves attention; the last two patients were given calcium lævulinate in a dose of 3 g. per 24 hours, and this produced a moderate rise in serum-calcium level. Hypophosphatæmia was also demonstrated but no attempt was made to correct it. The serum magnesium and sulphate were not studied. The body temperature tended to be slightly subnormal during treatment. Four patients (cases 3, 4, 9, and 14) were psychotic for a few days after becoming conscious.

Complications

1. The venous pressure in the external jugular vein usually rose during the first 2–3 hours of treatment.

In one patient (case 8) transient pulmonary œdema developed 2 hours after the diuretic therapy was begun. She had had an acute myocardial infarction a month previously. During the 20 hours after admission and before treatment, 1·5 litres of blood and plasma substitute was given. A radiograph of the lungs before therapy showed pulmonary vascular congestion. The pulmonary œdema disappeared after the head end of the bed was raised and positive-pressure breathing was started, and it did not recur during treatment, which was continued for 40 hours afterwards.

2. The most severe complications encountered were acute dehydration and intracranial hæmorrhage.

One patient (case 12) was a woman of 65, weighing less than 6 stone who was intoxicated with ethylallyl barbiturate. She was hypothermic (92°F) on admission, and had the exceptionally high serum-barbiturate value of 35·4 mg. per 100 ml. The diuresis became excessive (1500 ml. per hour) and the rectal temperature dropped to 88°F. 5 hours after starting the diuretic treatment. The standard solution containing glucose was continued intravenously to balance the urinary output. Without fluid deficit severe acute dehydration was observed, with low blood-pressure and decreased pressure in the anterior chamber of the eyes. The excessive diuresis continued even though the urea infusion was discontinued temporarily, apparently because of gross glucosuria (above 1 g. per 100 ml.). The addition of insulin (20 i.u. per litre) did not reduce the urinary output in the next hour. A glucose-free hypotonic electrolyte solution was then given by stomach-tube, whereafter the diuresis rapidly decreased. Urea infusion was then continued along the usual lines, insulin being added to all glucose-containing fluids. Gross glucosuria did not recur, and osmotic diuresis was maintained at the usual level of about 500 ml. per hour for 71 hours. This patient did not regain consciousness as did the others. 5 days after admission, when the barbiturate was almost completely eliminated, she showed confusion, seizures, and decreased movement of the left limbs. Lumbar puncture showed slightly hæmorrhagic cerebrospinal fluid. Some weeks later complete clinical remission gradually ensued. This most unusual sequel of barbiturate poisoning—intracranial hæmorrhage—seems to have been due to the transitory severe acute dehydration. Cases 13 and 14 also had glycosuria (0·1–1·0 g. per 100 ml.); when insulin was added to the intravenous fluid glycosuria disappeared in case 13 but it continued moderately in case 14. The risk of glycosuria causing excessive polyuria seems to limit the degree of diuresis which can safely be induced, but this undoubtedly varies from one patient to another. In this series the diuresis has usually not been allowed to exceed 800 ml. per hour—i.e., about 20 litres per 24 hours.

Calculations

After a period of reabsorption from the gastrointestinal tract, the serum-barbiturate concentration decreased approximately mono-exponentially both in treated patients and in the untreated controls, thus:

$$(1)\quad C(t) = i_0 e^{-kt}$$

where

C(t) is the serum-concentration of the compound at time t.
i_0 is the initial serum-concentration—i.e., the concentration after which a steady decrease in plasma-concentration is noted.
e is the base of the natural logarithm.
k is the elimination constant (in days^{-1}).
t is the time, in days, measured from the time, t_0, at which i_0 is observed.

No indication of a change of tolerance was noted—i.e., the patients regained consciousness at about the same serum-barbiturate level as did the controls. This agrees with the results of Lous (1945c), who found no evidence of acute tolerance. Accordingly one may assume that there exists for any given patient a serum-barbiturate level, A, at which the patient regains consciousness. Let T be the time required for awakening the patient—i.e., the time in days (reckoned from t_0) before C(t) reaches A. Then for control (c) and diuresis treatment (d) the identical relations hold:

$$(2)\quad A = i_0 e^{-kc \cdot Tc} = i_0 e^{-kd \cdot Td}$$

The effect, E, of the treatment on shortening the period of unconsciousness may be defined as the ratio of the length of unconsciousness in the untreated control (Tc) to that of the treated patient (Td).

$$(3)\quad E = \frac{Tc}{Td} = \frac{kd}{kc}$$

In this study the elimination-rates (R) have been expressed as the percentage daily decrease in plasma-level, thus:

$$R = \frac{(i_0 e^{-kt} - i_0 e^{-k(t+1)}) \cdot 100}{i_0 e^{-kt}}$$

or

$$k = -\ln(1 - R/100)$$

Hence the effect, E, can be calculated as:

$$(4)\quad E = \frac{\ln(1 - Rd/100)}{\ln(1 - Rc/100)}$$

where E, by definition, is the number of times the period of unconsciousness has been shortened, and Rd and Rc are the daily elimination-rates under diuretic and control conditions respectively.

Results

Preliminary studies showed that the urinary clearance of barbiturate increased considerably with increasing

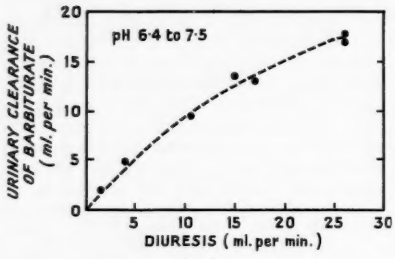

Fig. 1.

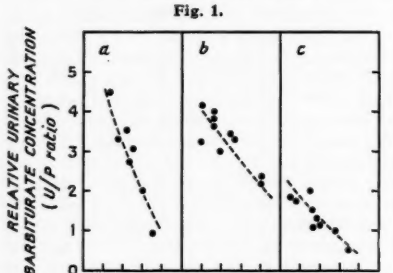

Fig. 2.

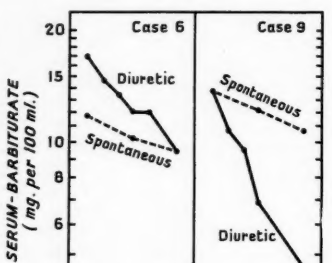

Fig. 3.

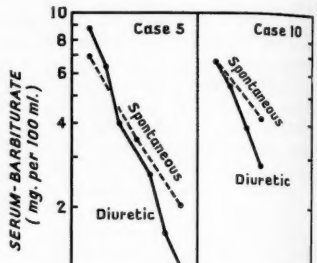

Fig. 4.

Fig. 1—Effect of variations in diuresis on urinary clearance of phenylethyl barbituric acid.

Fig. 2—Effect of variations of urinary pH on the relative urinary barbiturate concentration in three patients poisoned with (*a*) allylisopropyl, (*b*) diethyl, and (*c*) phenylethyl barbituric acid. The diuresis was about 2 ml. per min.

Fig. 3—Two patients with repeated phenylethyl-barbituric-acid intoxication.

Case 6: spontaneous excretion-curve in August, 1959; diuretic treatment in September, 1959.

Case 9: spontaneous excretion-curve in August, 1959; diuretic treatment in November, 1959.

Fig. 4—Two patients with repeated allylisopropyl-barbituric-acid intoxication.

Case 5: spontaneous excretion-curve in April, 1955; diuretic treatment in August, 1959.

Case 10: spontaneous excretion-curve in March, 1954; diuretic treatment in November, 1959.

diuresis at a constant urinary pH (fig. 1), and that alkalinisation enhanced the excretion at any given diuretic level (fig. 2). The renal filtration-rate, as measured by creatinine-clearance, did not influence the excretion of barbiturate in this series: the relative urinary barbiturate concentration (U/P ratio in table I) was not significantly lower in the patients with subnormal renal filtration-rate.

The various barbiturate compounds differed with respect to their renal excretion. At a diuretic level of about 8 ml. per min. and a urinary pH of 8·0–8·4, the U/P ratio in patients with normal renal function was 0·9–3·0. The total excretion of barbiturate in the urine also varied with the serum-barbiturate level and the length of treatment. 0·9–9·6 g. was recovered in the urine during treatment (table I).

The overall elimination-rate of barbiturate from the body was always increased during diuretic treatment. Four patients had previously been observed in the same department for intoxication with the same barbiturate for which they were later given diuretic treatment. Hence it was possible to use these patients as their own controls. Increased amounts of barbiturate were eliminated during diuresis in all four cases (figs. 3 and 4).

In the group as a whole the elimination of barbiturate from the blood (% per 24 hours) was compared with that in the untreated controls (table II).

Eleven control patients with diethyl-barbituric-acid intoxication averaged 17% elimination per 24 hours (compare the value of 10–15% found by Lous [1954c]). Eight control patients who had taken equal amounts of diethyl and allyl-isopropyl barbituric acid showed 20% elimination per 24 hours (fig. 5). The control value for ethylallyl barbiturate was taken from Lous (1954c), who found a 24-hour elimination of 25–30% in five cases. Sixteen control patients with allyl-isopropyl-barbituric acid intoxication showed an average elimination of 36% per 24 hours (compare Lous' value of 30–40%). Seven control patients with phenylethyl - barbituric - acid intoxication had an average elimination-rate of 16% per 24 hours (Lous' figure was 10–15%). The control value for diallyl-barbituric-acid intoxication was that of Lous (1954c), who found an average 24-hour elimination 26% in eleven patients.

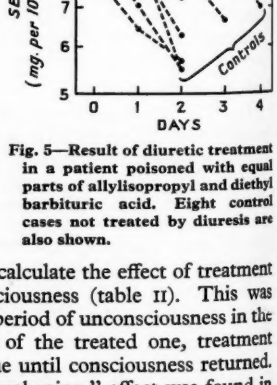

Fig. 5—Result of diuretic treatment in a patient poisoned with equal parts of allylisopropyl and diethyl barbituric acid. Eight control cases not treated by diuresis are also shown.

These data permit one to calculate the effect of treatment on the length of unconsciousness (table II). This was defined as the ratio of the period of unconsciousness in the untreated patient to that of the treated one, treatment being supposed to continue until consciousness returned. The most pronounced "awakening" effect was found in intoxication with diethyl, diethyl + allylisopropyl, and ethylallyl barbituric acid where the period of unconsciousness was reduced by a factor of about 3. Diuretic treatment in phenylethyl and allyl-isopropyl-barbituric-acid intoxication reduced the period of unconsciousness by

TABLE II—EFFECT OF FORCED DIURESIS AND ALKALINISATION OF THE URINE IN SEVERE ACUTE BARBITURATE POISONING

The shortening effect on the period of unconsciousness was calculated as in the appendix.

Barbiturate compound	Average elimination-rate (% per 24 hr.)		Effect on the period of unconsciousness
	Treated	Control	
Diethyl	47	17	3·4
Diethyl + allylisopropyl ..	51	20	3·2
Ethylallyl	61	28	2·9
Allylisopropyl	60	36	2·1
Phenylethyl	29	16	2·0
Diallyl	34	26	1·4

a factor of about 2. The diuretic treatment was least efficient in a case of diallyl-barbituric-acid intoxication, where the period of unconsciousness was only reduced by 1·4.

These calculations of the effect of diuretic treatment on length of unconsciousness require that the drug is completely absorbed from the gastrointestinal tract before treatment is started. If this is not so, the effect cannot be calculated. If the drug is not completely absorbed (fig. 6) the diuretic treatment can still be assumed to reduce the level of anæsthesia as well as to shorten the period of unconsciousness.

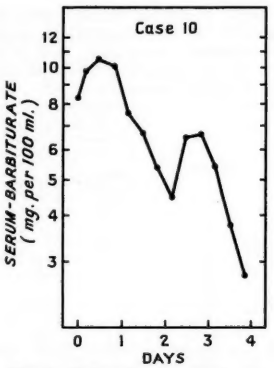

Fig. 6—Delayed intestinal re-absorption in a patient with acute allylisopropyl-barbituric acid-poisoning.

Diuretic treatment was continued for 92 hours, during which the urinary volume was 46·7 litres, and 5 g. of barbiturate was excreted.

Discussion

That increased excretion of barbiturates in the urine results from increasing the urinary output has long been known (see, for example, Johnson et al. 1930, Gower and Van de Erve 1933, Koppanyi et al. 1933, 1934, Lous 1954b). Waddell and Butler (1957) first showed the effect of variations in urinary pH. In general, however, clinicians have hesitated to apply this experimental knowledge to the treatment of patients with acute intoxications—presumably because of the desire to avoid overhydration, and because of the lack of dramatic clinical effect from a moderate increase of diuresis.

In 1949 Ohlsson introduced his "blood lavage" therapy: he reported three cases in which the infusion of isotonic fluid intravenously (combined with mercurial diuretics) was well tolerated, and caused a diuresis of about 5 litres per 24 hours. No alkalinisation was used. Ohlsson argued correctly that the experimental evidence of other investigators indicates that diuretic therapy is likely to shorten the period of unconsciousness. He has continued to use this therapy (Ohlsson 1959), and it is also being used in other clinical centres (e.g., Fontan et al. 1958).

Mollaret et al. (1959), independently of Waddell and Butler (1957), observed the enhancing effect of alkalinisation on the urinary excretion of phenylethyl-barbituric acid. Both groups of investigators also found that an alkaline shift in arterial pH caused moderate increase of plasma-barbiturate level, reflecting a small decrease in intracellular barbiturate concentration. On this basis Mollaret and his coworkers developed the "alkalinisation therapy" for acute barbiturate intoxication. Forty-seven patients were treated. On the average 3–4 litres of isotonic or hypotonic sodium-bicarbonate solution were given per 24 hours. Almost equally large urine-volumes were observed with a urinary pH of about 7 in forty patients treated with isotonic bicarbonate, and with a pH of about 8 in seven patients treated with hypertonic bicarbonate. All forty-seven recovered. By comparing the period of unconsciousness (relative to the ingested dose) with that of a control group in which no alkalinisation was used a moderate overall improvement was found. Reliable information about the ingested dose may be difficult to obtain, and the rate of absorption of the drug may vary. Hence this method of assessing the efficiency of therapy cannot give as much information as that used in the present study—namely, comparison of the 24-hour elimination-rates of barbiturate from the serum.

The cases reported here were treated with a combination of blood lavage and alkalinisation therapy. Using urea and sodium lactate, 11 litres of alkaline urine (pH 8·0–8·4) was obtained per 24 hours. In a few cases not included mannitol instead of urea was used as an osmotic load, but because this was more difficult to administer than urea it was abandoned. (Schlegel and Jørgensen [1959], who used osmotic diuresis for treating patients with extensive burns, had similar experience.)

The diuretic treatment is a form of dialysis utilising the body's own kidneys as dialyser. At a urinary flow of 8 ml. per minute and with alkaline urine, the renal clearance was about 13 ml. per minute. This may be compared with clearances of 30–40 ml. per minute obtained by artificial hæmodialysis in barbiturate-poisoned dogs (Sunshine and Leonards 1954) and in man (Berman et al. 1956). Thus diuretic therapy is roughly equivalent to using an artificial kidney for about 8 hours daily. Few reports on the clinical efficiency of artificial hæmodialysis in acute barbiturate intoxication have appeared (Alwall et al. 1952, Kyle et al. 1953, Berman et al. 1956). Continuous hæmodialysis for 24 hours or more, or repeated shorter dialysis is not easy to perform in critically ill patients; in particular, circulatory instability may be a decisive complication (as in cases 8 and 11 studied by Berman et al. 1956). The relative values of the two forms of active treatment—diuresis and hæmodialysis—cannot be evaluated in detail, however, since the number of cases treated by either technique is too small.

Conclusions

This report has aimed at demonstrating objectively that a clinically significant awakening effect may be produced by forced diuresis and alkalinisation of the urine. This was evident both with comparable controls and when the patient served as his own control. The period of unconsciousness was reduced to a half or a third. Hence the efficacy of these therapeutic principles seems to be established.

Before recommending this treatment for clinical use, however, its benefits and complications must be evaluated carefully. The severest complications encountered were transient pulmonary œdema in one case and severe dehydration in another. But the diuretic treatment was probably lifesaving in at least three patients (cases 4, 10, and 12). Changes in technical detail may be found to increase the safety and efficiency of the procedure, and to reduce the number of laboratory analyses necessary. On this basis, forced diuresis and alkalinisation is recommended in severe barbiturate poisoning. As emphasised by Mollaret et al. (1959) this method should not be regarded as an alternative but as an adjunct to the fundamental supportive therapy developed by Clemmesen and his coworkers (see the review by Clemmesen 1959).

The various cerebral depressants are all highly diffusible substances and thus they all pass the blood-brain barrier readily. Hence the renal clearance of all such substances can be assumed to increase as diuresis increases, while the effect of changes in urinary pH may vary. Acute poisoning with cerebral depressant drugs other than barbiturates may, therefore, be effectively treated by techniques similar to those used in the present study, provided the rate of endogenous elimination is sufficiently slow. In principle this has long been utilised in bromide intoxications,

where chloride administration increases the renal bromide-clearance.

Summary

Forced diuresis and alkalinisation of the urine were used to treat fourteen cases of very severe barbiturate intoxication (the maximal serum barbiturate concentration averaged 19 mg. per 100 ml.). Urea was used as the diuretic agent, and sodium lactate as the alkalising agent. About 11 litres of alkaline urine per 24 hours was produced during therapy, which lasted 42 hours on average.

The overall elimination-rate of barbiturate from the body was increased in all fourteen cases over that of comparable control cases. The most pronounced effect was in patients with diethyl, diethyl + allylisopropyl, and ethylallyl barbiturate intoxications; in these patients the period of unconsciousness was reduced to about a third. For allylisopropyl and phenylethyl barbiturate the reduction was about half. The least effect was seen in a case of diallyl intoxication, where the duration of unconsciousness was reduced by only 1·4.

I am greatly indebted to Chief Physician C. Clemmesen and his staff of doctors and nurses for valuable aid during this investigation; to Dr. P. Lous, chief of the department of clinical biochemistry, for his advice and help especially with regard to barbiturate analyses; and to Miss R. Schultz and her colleagues for practical assistance with the numerous laboratory analyses.

REFERENCES

Alwall, N., Lindgren, P., Lunderquist, A. (1952) *Acta med. scand.* **143**, 299.
Berman, L. B., Jeghers, H. J., Schreiner, G. E., Palotta, A. J. (1956) *J. Amer. med. Ass.* **161**, 820.
Clemmesen, C. (1959) *Dan. med. Bull.* **6**, 209.
Fontan, M. A., Couteau, J.-M., Lagarde, M. M., Berand, J. (1958) *J. Méd. Bordeaux*, **135**, 492.
Gower, W. E., Van de Erve, J. (1933) *J. Pharmacol.* **48**, 141.
Johnson, C. A., Luckhardt, A. B., Lighthill, J. A. (1930) *J. Amer. med. Ass.* **95**, 576.
Koppanyi, T., Murphy, W. S., Krop, S. (1933) *Arch. int. Pharmacodyn.* **46**, 76.
— — — (1934) *J. Pharmacol.* **52**, 223.
Kyle, L. H., Jeghers, H., Walsh, W. P., Doolan, P. D., Wishinsky, H., Palotta, A. (1953) *J. clin. Invest.* **32**, 364.
Lous, P. (1950) *Acta pharm. tox., Kbh.* **6**, 227.
— (1954a) *ibid.* **10**, 134.
— (1954b) *ibid.* p. 147.
— (1954c) *ibid.* p. 261.
Mollaret, P., Rapin, M., Pocidalo, J.-J., Monsallier, J.-F. (1959) *Pr. méd.* **67**, 1435.
Ohlsson, W. T. L. (1949) *Nord. Med.* **42**, 1471.
— (1959) Personal communication.
Schlegel, J. U., Jørgensen, H. (1959) *Ann. Surg.* **149**, 252.
Sunshine, I., Leonards, J. R. (1954) *Proc. Soc. exp. Biol., N.Y.* **86**, 638.
Waddell, W. J., Butler, T. C. (1957) *J. clin. Invest.* **36**, 1217.
Wright, I. T. (1954) *J. clin. Path.* **7**, 56.

HIGH BLOOD-PRESSURE AND STROKE

NECROPSY STUDY OF HEART-WEIGHT AND LEFT VENTRICULAR HYPERTROPHY

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WE have shown that narrowing of the vertebral artery is appreciably more closely associated with high blood-pressure than is narrowing of the internal carotid artery (Dickinson and Thomson 1959, 1960). We have also shown that in people who had died with strokes the fluid-carrying capacity of the main cerbral arteries was reduced, and that there was no difference in this respect between cerebral hæmorrhage and cerebral softening or infarction.

If these results are correct, strokes in the vertebral-artery territory should be associated with slightly higher blood-pressures than those in the internal-carotid-artery territory; and high blood-pressure should be as closely associated with cerebral softening and infarction as it is with cerebral hæmorrhage.

These two predictions have been tested by a retrospective necropsy series.

TABLE I—BREAKDOWN OF CASES, SHOWING TOTAL NUMBERS ANALYSED AND ACTUAL NUMBERS OF CASES OF CEREBRAL HÆMORRHAGE, CEREBRAL INFARCTION, AND FOREBRAIN AND HINDBRAIN STROKES (CASES FALLING INTO MORE THAN ONE GROUP ARE SHOWN IN SEPARATE COLUMNS)

Group	Strokes at all sites			Hæmorrhages and infarcts		
	Cerebral hæmorrhage	Cerebral infarct	Hæmorrhage and infarct both present	Forebrain lesion	Hindbrain lesion	Fore- and hindbrain lesions both present
All cases (340):*						
189 males ..	115	61	13	121	38	30
151 females	80	63	8	107	22	22
All cases with heart-weight recorded (335):†						
187 males ..	113	61	13	121	36	30
148 females	78	63	7	105	22	21

* Presence or absence of left ventricular hypertrophy analysed in table II.
† Heart-weights analysed in figs. 1–3.

Methods

The data were abstracted from the Middlesex Hospital necropsy records for the period 1931–59 inclusive. The records of all cases of brain damage were examined; and cases of malignant hypertension, trauma, cerebral tumour, bleeding diathesis, subarachnoid hæmorrhage from aneurysm, polyarteritis nodosa, and presumed embolism secondary to valvular heart-disease were rejected. This left 340 cases of cerebral vascular lesions, or strokes, in which there was no evidence of precipitating cause other than high blood-pressure or arterial degeneration.

The nature of the lesion was classified as *cerebral hæmorrhage* if blood was present, and as *cerebral infarction* in the presence either of cerebral softening or of " apoplectic " cysts. Both the latter conditions would have been diagnosed by the present clinical convention as " cerebral thrombosis ", although an actual thrombus was seen in only a few cases. The site of the lesion was noted as *hindbrain* if in the brain stem or occipital lobes, and as *forebrain* if in other areas. This distinction was chosen to delineate as closely as possible the normal territories of supply of the vertebral and of the internal carotid arteries.

The heart-weight was recorded for each case, and the records were also examined for the presence or absence of left ventricular hypertrophy. This was regarded as present when mentioned, whether the degree was slight, moderate, or gross, and as absent when not mentioned, even if the heart-weight was much above normal.

Results

Table I shows an analysis of the cases, in 5 of which no value for heart-weight had been recorded. Figs. 1–3 show the results obtained by comparing heart-weights in different groups, in the 335 available cases. The vertical interrupted lines indicate means for each group, and the horizontal lines crossing each represent the limits of ± twice the standard error of the mean. Fig. 1 compares heart-weights of cases of cerebral infarction with those of cerebral hæmorrhage. Cases where both lesions were found at necropsy (see table I) have been scored as $^1/_2$ case in each group, so that a true picture of heart-weight distribution in stroke should be obtained. The differences of the means are not affected. There is no significant difference in mean heart-weight as between cerebral hæmorrhage and cerebral infarct, and the trend is in the opposite direction in males and females. The pooled

significance for both sexes is just in favour of higher heart-weight in cerebral hæmorrhage, but the difference is negligible (c=0·294; 0·7 < P < 0·8).

A similar comparison for hindbrain to forebrain strokes is shown in fig. 2. Here the trends for each sex are stronger, and in the same direction. The pooled significance is probably significant (c for difference of means=2·209; P < 0·03).

Chauvenet's criterion has been used in calculating the differences of the means, to reduce the high variance created by the presence of a few cases of extremely high heart-weight. Class-by-class comparisons of the data of fig. 2 by χ^2 give results of the same significance as those derived from comparison of means. There is a strong tendency for heart-weight (which was measured in ounces) to be recorded in even rather than odd numbers, and this shows itself by alternate columns being larger than intervening columns. Fig. 3 shows the effect of summing pairs of adjacent columns of fig. 2, and reveals the shape of the normal distribution more clearly.

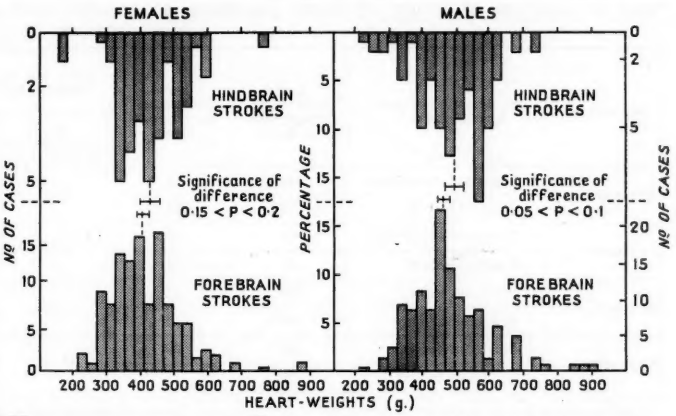

Fig. 2—A similar analysis of the same cases, but comparing hindbrain with forebrain lesions.

Table II shows the data from all the 340 cases, indicating the incidence of left ventricular hypertrophy in each group. None of the results is significant, but there is a trend towards a higher prevalence of left ventricular hypertrophy in cerebral hæmorrhage and in hindbrain strokes. The trend is in the same direction in both sexes, but is greater for males even allowing for the greater numbers of males. Left ventricular hypertrophy is less commonly recorded for all strokes in females—probably because it is more easily overlooked in the smaller female heart.

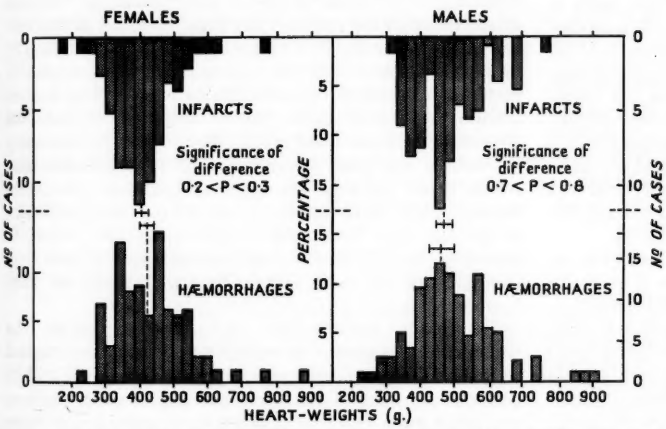

Fig. 1—Analysis of the 335 available cases, in terms of heart-weight, sex, and occurrence of cerebral hæmorrhage or cerebral infarction.

Cases falling simultaneously into both latter groups have been scored as $^1/_2$ case in each. The actual numbers in each group are indicated on the outside vertical scales; the central v rtical scale indicates percentages of the total of each group. The interrupted lines indicate mean heart-weight of each group (calculated after application of Chauvenet's criterion) and also show the limits of ± twice the standard error of the mean. Although the scales of heart-weight are in grammes, the columns represent ounces (units of 28·3 g.) since this was the original form of the data.

Discussion

Two main conclusions can be drawn from this study. The first is that the heart-weight is probably greater on average in people with hindbrain as opposed to forebrain strokes. Statistically this conclusion has a 1 in 30 chance of error. There is a slighter tendency for the prevalence of left ventricular hypertrophy to be increased also, but this is not significant.

The second conclusion is that it is difficult to demonstrate any difference between the hearts of people with cerebral hæmorrhage and cerebral infarction. The heart-weights are the same; and although the results suggest a higher prevalence of left ventricular hypertrophy in cerebral hæmorrhage, these results may be due to observer error. If some of the pathologists who made the necropsy reports believed in a special association between cerebral hæmorrhage and very high blood-pressure, they might have noticed and recorded minor degrees of left ventricular hypertrophy more frequently. Alternatively, it

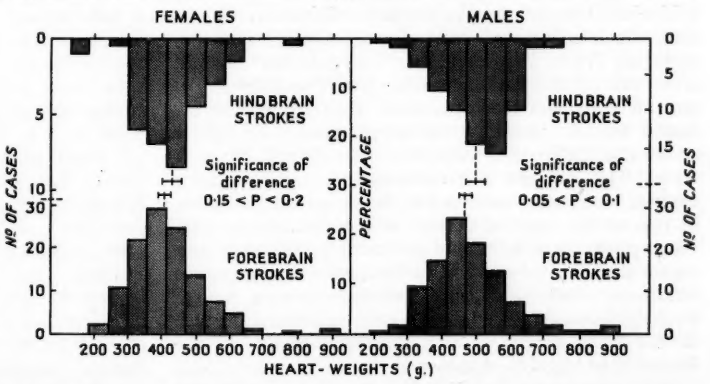

Fig. 3—The same analysis as in fig. 2, showing the effect of summing pairs of adjacent columns.

TABLE II—ANALYSIS OF GROUPS OF CASES, ACCORDING TO WHETHER LEFT VENTRICULAR HYPERTROPHY WAS RECORDED OR NOT RECORDED

No. and sex	Site or nature of lesion in brain	Left ventricular hypertrophy present	Left ventricular hypertrophy absent	Individual results for males and females, calculated separately		Results for the data of both sexes, calculated separately but pooled for significance	
				χ^2 (1 degree of freedom)	Significance	χ^2 (both sexes) (2 degrees of freedom)	Significance
189 males ..	Cerebral hæmorrhage	104½	17	3·685	0·05<P<0·1	4·292	0·1<P<0·2
	Cerebral infarct	50½	17				
151 females ..	Cerebral hæmorrhage	66	18	0·607	0·3<P<0·5		
	Cerebral infarct	49	18				
189 males ..	Forebrain lesions	108½	27½	1·636	0·2<P<0·3	1·797	0·3<P<0·5
	Hindbrain lesions	46½	6½				
151 females ..	Forebrain lesions	89	29	0·161	0·5<P<0·7		
	Hindbrain lesions	26	7				

Cases occurring in two groups at once (e.g., the simultaneous occurrence of cerebral hæmorrhage and infarction in the same patient) have been counted as ½ case in each group. This slightly reduces the significance of the results, but allows a rather more accurate figure to be given for the prevalence of left ventricular hypertrophy in the groups.

is remotely possible that the selection of cases may have obscured a real relationship, since cerebral hæmorrhage was usually the immediate cause of death, whereas cerebral infarction was sometimes an incidental finding. It is also possible that the increased heart-weight in most cases of cerebral infarction may be due to intrinsic heart-disease rather than to left ventricular hypertrophy consequent on high blood-pressure. There are many possible interpretations; but in view of the differences between the sexes, and the failure to show any difference in heart-weight, we are inclined at present to attribute the trend—it is a real one—to observer error. Such errors should not have influenced heart-weight, since this is customarily recorded by the postmortem-room technicians, who record the weight of all the organs.

We have not found any clear reported evidence to enable this point to be settled; but two lines of evidence suggest that the prevalence of hindbrain strokes in people with high blood-pressure may be real. Dorothy Russell (1954) found a predominance of pontine (hindbrain) lesions in her series of cerebral hæmorrhage in people with more severe grades of hypertension (" malignant and nephritic " group). In this group there were 54 forebrain and 21 hindbrain lesions (cases of unclassified meningeal hæmorrhage excluded), and in the group of benign hypertension there were 122 forebrain and 29 hindbrain lesions. Statistically this trend has a 1 in 8 chance of error. She ascribed the result to the prevalence in malignant hypertension of fibrinoid necrosis in the small arteries of the brainstem; but the trend is similar to that shown by our data, which excluded all cases of malignant hypertension. Saltzman (1959) has found that the posterior cerebral artery fills more commonly during carotid angiography in patients with high blood-pressure. He suggests that his results are not significant, but examination of his figures shows that the trend revealed has only a 1 in 8 chance of error. This suggests that the pressure in the posterior cerebral and basilar arteries may be lower, relative to that in the middle cerebral artery, in the presence of high blood-pressure, which would presumably predispose to a higher than normal incidence of ischæmic damage in the hindbrain. Collectively, the available evidence, though not impressive individually, does suggest a real difference in the blood-supply of the hindbrain relative to the forebrain in high blood-pressure.

It is commonplace to see severe aortic, coronary, and femoral atheroma without high blood-pressure; yet atheroma of the cerebral arteries severe enough to cause a stroke is very closely associated with high blood-pressure in all population studies (Stamler 1958). The available evidence seems to fit best with the recent suggestions of Dickinson and Thomson (1959) that " essential " hypertension may be the result rather than the cause of narrowing of the main cerebral arteries. The predominance of hindbrain strokes in severe hypertension fits in with our emphasis of the role of the vertebral arteries; but further studies on a larger series will be necessary to establish strongly significant differences. It will also be necessary to exclude any possible influence of selection-rate bias, which could produce an apparent spurious correlation between high blood-pressure and strokes in the hindbrain, if people with hindbrain stroke came less often to necropsy than did those with forebrain stroke, and were brought into the series only by the severity of their hypertension.

Correlation analysis can prove nothing except the presence or absence of association; and our original perfusion study and the work reported here could still be entirely explained if the vertebral and to a lesser extent the other main cerebral arteries were intrinsically more susceptible to damage by high blood-pressure than arteries in other regions. We think this unlikely, if only because natural selection, at least in men, might have been expected to produce the opposite result.

Summary

340 patients died in the Middlesex Hospital with spontaneous cerebrovascular accidents between 1931 and 1959 inclusive. Their records have been inspected; and it has been found that on average those with hindbrain strokes had greater heart-weights than those with forebrain strokes. There was a slightly higher prevalence of left ventricular hypertrophy in the cases of hindbrain stroke, but this was not significant. No significant difference was found in the heart-weight or in the prevalence of left ventricular hypertrophy as between cerebral hæmorrhage and cerebral infarction.

These results, together with other evidence, support our previous work, which suggested that narrowing of the main cerebral arteries (particularly the vertebral arteries in their cervical course) had a primary causal role in benign " essential " hypertension. These results also support the conception that cerebral hæmorrhage and cerebral infarction both have the same cause.

We are grateful to Prof. A. Kekwick for helpful criticism. This work was done while one of us was holding a Leverhulme research scholarship, and we are grateful for facilities provided in the Institute of Clinical Research.

REFERENCES

Dickinson, C. J., Thomson, A. D. (1959) *Lancet*, ii, 46.
— — (1960) *Clin. Sci.* **19**, 513.
Russell, D. S. (1954) *Proc. R. Soc. Med.* **47**, 689.
Saltzman, G-F. (1959) *Acta radiol., Stockh.* **52**, 1.
Stamler, J. (1958) *in* Cerebral Vascular Diseases (edited by C. H. Millikan); p. 98. New York.

FREE LYSINE EXCRETION IN PREGNANCY

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PREVIOUS investigations have shown the importance of protein in pregnancy (Bolton 1958) and particularly in certain pregnancy diseases (Bolton and Forster 1959).

In 1952 a patient was seen, with vomiting of late pregnancy, who had a falling serum-albumin without proteinuria. This suggested examination of the urine for abnormal aminoaciduria, and, through the courtesy of the Walter and Eliza Hall Institute for Medical Research, Miss Sarah Weiden demonstrated by paper chromatography that this was present. She examined a further nine specimens from pregnant women and found a wide range in both the amount and the variety of aminoacids excreted. The implication is that, besides the need for adequate protein intake, in some pregnancy diseases abnormal protein metabolism may have to be considered.

Preliminary qualitative studies were later made of the free aminoacids excreted during pregnancy. Duplicate chromatograms were run on 24-hour specimens of urine from nine pregnant and fifteen non-pregnant women. Of all the aminoacids excreted, the greatest variation was shown by lysine. This is not surprising; for lysine is not involved in deamination-reamination reactions, does not indulge in transamination, and is not attacked by aminoacid oxidases. It is likely, therefore to reflect changes in the utilisation and excretion of aminoacids more accurately than others less stable.

Attention was therefore directed towards developing a method for the quantitative estimation of lysine in urine (Kerley 1959), and this was then used to determine lysine excretion in 24-hour urinary samples. Urinary collection was checked by creatinine determinations and was found to be remarkably constant.

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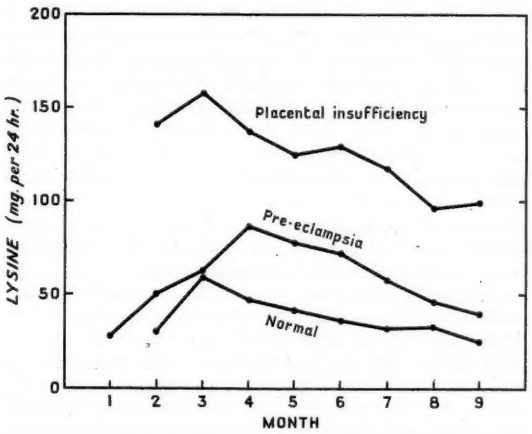
URINARY FREE LYSINE EXCRETION IN MG. PER 24 HOURS

Group	Case	Month								
		1	2	3	4	5	6	7	8	9
I Normal pregnancy	A	..	24	22	54	16	40	28	42	24
	B	..	..	74	66	62	68	30	52	25
	C	..	20	50	24	13	20	31	0	36
	D	..	..	88	72	..	..	..	..	0
	E	..	..	30	44	66	47	54	36	32
	F	..	48	53	32	37	34	38	22	24
	G	..	..	..	50	60	50	..	29	15
	H	..	..	..	..	28	..	0	29	..
	I	0	0	85	32	40	26	33	38	36
	J	..	44	73	60	21	30	23	35	..
	K	..	55	76	50	74	32	60	53	38
II Pre-eclampsia	L	36	42	62	..	40	..	34	36	43
	M	..	..	..	..	60	19	10	36	32
	N	17	50	36	122	114	73	62	18	13
	O	..	..	..	82	72	103	33	157	..
	P	..	..	44	118	200	168	147	..	82
	Q	..	50	21	38	18	52	38	34	50
	R	..	..	55	42	93	113	70	18	34
	S	..	..	172	164	62	51	88	51	28
	T	..	60	34	36	40	24	32	26	28
III Placental insufficiency	U	..	..	..	..	95	130	124	80	105
	V	..	56	92	96	110	102	90	84	38
	W	..	228	234	178	170	154	136	126	156
IV Urinary infection	AB	..	0	0	13	28	0	23	0	20
	CD	..	..	..	40	66	70	76	62	64
	EF	..	..	..	..	0	..	0	..	0
Labile hypertension	GH	..	..	..	..	22	44	0	0	..
	IJ	..	64	142	44	42	50	74	56	52
Threatened abortion	KL	..	26	52	42	62	68	76	50	36
Anæmia	MN	..	..	76	52	56	65	67	62	21
	OP	..	..	18	20	26	29	10	30	0



Investigation

Cases were handled and defined as previously described, (Bolton and Forster 1959), except that only patients in early pregnancy were referred and 24-hour specimens were obtained at approximately monthly intervals. Lysine excretion changes considerably after delivery, and for this reason duration of pregnancy was calculated back from this date. No delivery was thought to have been premature or postmature.

Thirty-one pregnant women were studied and specimens were also obtained from fifteen non-pregnant controls. Of the latter, not all were necessarily normal for some were receiving treatment in the gynæcological wards. The pregnant patients fell into four main groups; normal pregnancy (11); pre-eclampsia (9); placental insufficiency (3); and various other complications including urinary infection, anæmia, labile hypertension, and threatened abortion (8).

The daily lysine excretion in the controls ranged from 0 to 50 mg. with a mean of 30 mg. The excretion in pregnancy is shown in the table and for the separate groups of complications in the figure. Statistical analysis shows very considerable difference between these groups, and these differences can be detected as early as the sixteenth week. In general, there was a rise to a maximum level at approximately three months followed by a gradual fall to delivery. The three groups maintained their relative positions in excretion throughout, with placental insufficiency showing the highest levels and normal pregnancy the lowest. In the fourth unspecified group lysine excretion was consistently low.

Discussion

Paton and Wellby (1953) and Poidevin (1954), using paper chromatography, found no significant alteration in the urinary aminoacid excretion in pregnancy. Other workers (Christensen et al. 1957, Ruttinger et al. 1954, Miller et al. 1954) have demonstrated a considerable increase in the excretion of a number of free aminoacids including lysine. Christensen et al. (1957) studied three healthy women in the third and fourth month of pregnancy, and, using ion-exchange chromatography, found that the lysine output had increased four-fold. Ruttinger et al. (1954), using microbiological methods, found also a four-fold increase in lysine with one patient during three successive pregnancies. Miller et al. (1954) studied fifteen patients and obtained for lysine excretion a range from 15·6 to 249 mg. per 24 hours. The fluctuation in lysine excretion shown by this investigation is probably due to their not following any one patient through her pregnancy, each of their results being from a different woman.

Our results suggest that increased lysine excretion in pregnancy may be related to certain pregnancy diseases. Further discussion would be speculative, but aminoacid metabolism in pregnancy seems to require further investigation. Because changes appear early, they could be of particular clinical importance.

We would like to thank Prof. Charles Dent, of University College Hospital, London, for his helpful criticism, and for calling our attention to the existence of hereditary high lysine excretors. Patient W could be an example of this, for 3 months post partum she excreted 80 mg. of lysine daily and at 18 months 180 mg.

REFERENCES

Bolton, J. H. (1958) *Med. J. Aust.* i, 5.
— Forster, F. M. C. (1959) *ibid.* i, 361.
Christensen, P. J., Date, J. W., Schonheyder, F., Volqvartz, K. (1957) *Scand. J. clin. lab. Invest.* **9**, 54.
Kerley, L. F. (1959) *J. Lab. clin. Med.* **53**, 149.
Miller, S., Ruttinger, V., Macy, I. G. (1954) *J. biol. Chem.* **209**, 795.
Paton, J. B., Wellby, M. L. (1953) *Med. J. Aust.* ii, 639.
Poidevin, L. O. S. (1954) *ibid.* i, 105.
Ruttinger, V., Miller, S., Andrecovich, M. B., Perdue, G. M. (1954) *Proc. Soc. exp. Biol., N.Y.* **86**, 108.

A LOCAL-ANÆSTHETIC SOLUTION WITH LONGER ACTION

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ONE of the benefits of modern general anæsthesia is the early awakening of the patient. This allows deep breathing and coughing to begin before secretions accumulate in the bronchial tree. Unfortunately some operation wounds are so painful that analgesic drugs have to be given at once, reducing the cough reflex and depressing respiration. In an attempt to produce local, as distinct from general, analgesia, local anæsthetics have sometimes been injected at the end of the operation, either around the wound or in the sensory nerve pathways. There is, however, no safe or reliable long-acting local anæsthetic solution (Bryce Smith 1960).

After a number of experiments I discovered that 1% lignocaine in 10% 'Dextraven' (Bengers) with 1/250,000 adrenaline produced local analgesia for 10 hours. (10% dextraven is 10% dextran and 5% glucose in water.) Using subcutaneous injections of 1 ml. of 1% lignocaine with and without the other components of the mixture, the average periods of analgesia to pin prick were:

Lignocaine	1 hour
Lignocaine with 1/250,000 adrenaline	$2^1/_2$ hours
Lignocaine in 10% dextraven	6 hours
Lignocaine in 10% dextraven with 1/250,000 adrenaline	10 hours

It was noticed that the area of anæsthesia produced by the lignocaine alone was considerably larger than that produced by the lignocaine-dextraven solution. As there were no complications at the site of injection, a clinical trial of the 1% lignocaine-dextraven solution was undertaken.

Methods

Preparation of the solution—0·5 g. lignocaine is stirred into 50 ml. 10% dextraven, placed in a 50 ml. bottle, autoclaved at 10 lb. pressure for 30 minutes, and sealed with a rubber cap. 0·2 ml. of 1/1000 adrenaline is added just before the solution is used.

Operations.—Thoracic and abdominal incisions and hæmorrhoidectomy operations were chosen for study, as being particularly painful.

Injections.—(1) For upper-abdominal incisions, the rectus muscle and the subcutaneous edges of the wound were infiltrated with the solution by the surgeon after he had closed the peritoneum. (2) For thoracic incisions the surgeon injected, from inside the thoracic cavity, 5 ml. of solution into the intercostal space posterior to the excised rib or where the periosteum had been stripped from a rib, and also into the intercostal space above and below. These ribs are often cracked by the rib-spreader. 5 ml. was injected through the skin, into the intercostal space, immediately posterior to the drainage tube. The posterior 3 in. above and below the wound was injected subcutaneously just before the skin sutures were inserted. (3) For hæmorrhoidectomies the subcutaneous tissue around the anus and the anal sphincter were infiltrated with varying amounts of the solution.

Criterion of relief.—The nurses were asked to give a post-operative analgesic drug when they thought it was needed. The length of time between the patient returning to the ward and the giving of an analgesic was used as the gauge of success.

Results

There were no immediate reactions, general or local, after the injections and no wound sepsis developed.

Upper-abdominal Incisions (30 patients)

Laparotomies (6).—Five patients had 40 ml. of the solution injected (20 ml. into the rectus muscle and 20 ml. subcutaneously). Of these, three did not require any postoperative analgesia, and two needed analgesic drugs at 6 and 10 hours because of wound pain. One patient had 20 ml. injected (10 ml. into rectus and 10 ml. subcutaneously) and needed an analgesic at 4 hours because of wound pain.

Gallbladder, common-bileduct and peptic-ulcer operations (24).—Seventeen patients had 40 ml. of the solution injected (20 ml. into the rectus muscle and 20 ml. subcutaneously). Of these, three did not need any postoperative analgesia. Two needed an analgesic at 17 and 19 hours because of shoulder pain. Eight needed an analgesic at 6, 6, 7, 7, $8^1/_2$, $9^1/_2$, 10, and 12 hours because of wound pain. Two needed sedation at 2 and 4 hours because of restlessness, and two needed an analgesic at $2^1/_2$ hours because of an aching pain inside the abdomen. Two patients had 20 ml. injected into their subcutaneous tissues only: one of them needed an analgesic at $1^1/_2$ hours because the wound ached and the other at 10 hours because of pain in the wound. Three patients had 15 ml. injected subcutaneously only, and needed analgesic drugs at $1^1/_2$, $4^1/_2$, and 8 hours because of wound pain.

Thoracotomies (11 patients)

All these patients were injected with 40 ml. Two mitral valvulotomies, two hiatal-hernia repairs, one pneumonectomy, one excision of empyema and decortication, one excision of œsophageal stricture and anastomosis, one lung biopsy, and one excision of parietal pleura needed an analgesic because of wound pain at 5, 7, 9, 11, 6, 7, 16, 5, and 7 hours. One aortic valvulotomy required analgesia after 4 hours because of a cramp-like pain in the shoulder, and one obliteration of emphysematous lower lobe needed mild analgesia because of pain in the back at 6 hours.

Hæmorrhoidectomies (7 patients)

Five patients received injections of 40 ml. Of these, four patients did not require any postoperative analgesia and one patient needed an analgesic at 8 hours because of a dull ache around the anus. One patient received 20 ml. and needed analgesia at 3 hours because of a " pricking " sensation around the anus; and one received 15 ml. and needed analgesia at 9 hours because of abdominal discomfort.

The patients undergoing intrathoracic operations and hæmorrhoidectomy were clearly benefited by the injection. The wound of the chest wall was free of pain; the patients were pink and could take deep inspirations, and they were comfortable for some hours. The hæmorrhoidectomies were perhaps the most spectacular, since the patients were free of pain on return to the ward and four out of seven remained so, the rest only feeling minor discomfort. The intra-abdominal operations were benefited to the extent that, if enough solution was carefully injected into the rectus muscle and the subcutaneous tissue, the wound remained pain-free for some hours and then hurt relatively little. If no severe intra-abdominal operation was performed, the patients were quite comfortable; but, if an operation was carried out, the patients had an ill-defined uneasy feeling inside their abdomen.

As the effect of this solution on the cerebrospinal fluid or the spinal cord has not yet been studied, no extradural injections have been given.

Summary

Subcutaneous injection of a 1% solution of lignocaine in 10% 'Dextraven' with 1/250,000 adrenaline produced analgesia for 10 hours.

When injected around operation wounds to block sensory nerves, it considerably reduced the need for other analgesics in patients who had undergone thoracic or upper-abdominal operations or hæmorrhoidectomy. The patients were consequently able to breathe and cough more freely.

I wish to thank the surgeons at Peterborough Hospital and at the East Anglian regional thoracic surgical centre at Papworth for giving the injections and for their encouragement. Also Miss T. Robertson, chief pharmacist to Peterborough Hospital, and her staff for so willingly making up the solutions.

REFERENCE

Bryce-Smith, R. (1960) *Brit. med. J.* i, 1039.

SIMPLIFIED METHOD FOR DETECTING FORMIMINOGLUTAMIC ACID IN URINE AS A TEST OF FOLIC-ACID DEFICIENCY

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IN 1951 a glutamic-acid precursor was detected in the urine of folic-acid-depleted rats (Bakerman et al. 1951). A similar substance, formed by the enzymatic degradation of histidine, was identified as formamidino-glutaric acid (formiminoglutamic acid; FIGLU) by Borek and Waelsch (1953). It proved to be identical with the substance found in rat urine by Seegmiller et al. (1954). This compound, which normally reacts with tetrahydrofolic acid in intermediary metabolism, accumulates when folic acid is deficient. Histidine is a precursor of FIGLU in the body and has been administered to increase its excretion (Tabor et al. 1953). Excessive FIGLU excretion after oral histidine has been reported in folic-acid-deficient patients, and has been used as a test for this deficiency (Luhby et al. 1959a and b, Spray and Witts 1959). However, the methods of giving histidine have varied from 15 g. daily in divided doses before meals to a single dose of 2 g. which is about the normal dietary intake (Block and Bolling 1951).

The methods for detecting and estimating FIGLU also vary:

The most sensitive is enzymatic (Tabor and Wyngarden 1958) and will detect 0·1 μg. per ml. urine; but the enzyme is laborious to prepare and the estimation takes some 5–6 hours. A microbiological method is less sensitive and probably less specific detecting about 10 μg. per ml. urine and taking 3–4 days. A more elaborate method combines these two procedures (Silverman et al. 1958), but seems to offer no advantages, whilst paper chromatography (Luhby et al. 1959a) is specific but less sensitive and only detects 20–50 μg. per ml. urine.

A normal person apparently excretes up to 30 μg. per ml. urine and this is not increased after taking 15 g. histidine daily for 3 days. In folic-acid deficiency these amounts rise to as much as 275 μg. per ml., but the majority are normal without histidine loading. After histidine loading FIGLU increases from 90 to 1909 μg. per ml. urine (Luhby et al. 1959a and b).

There is need for a reliable and rapid test of folic-acid deficiency. We report here a highly specific method of detecting FIGLU using high-voltage electrophoresis. This is rapid and more sensitive than the chromatographic method, since small molecules will move in compact masses under these conditions.

Materials and Methods

FIGLU was prepared by the method of Tabor and Rabinowitz (1957) and was used as a standard substance throughout.

25 μl. of urine was run on Whatman no. 3 MM. paper at 6·0 kV and 60–80 amp. for 20 min. under electrophoretic conditions described by Westall (1960), using a buffer of pyridine-acetate (50 ml. pyridine + 20 ml. glacial acetic acid to 5 litres with water) at pH 5·4. Urines were run alone and containing a known quantity of FIGLU marker. The spots have been detected by two methods:

In one, the paper was sprayed with the nitroprusside-ferricyanide reagent (Kirby-Berry et al. 1951), when FIGLU gives an orange-red stain directly.

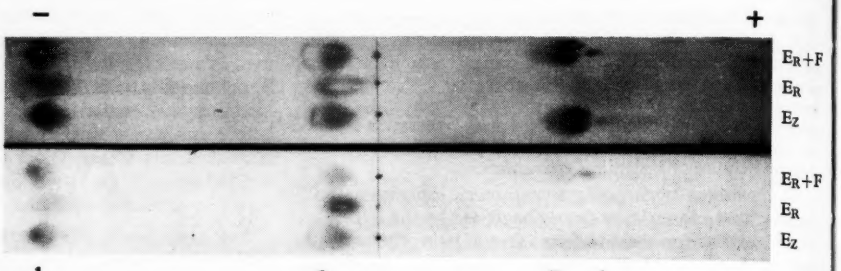
In the other, duplicate papers were run, after which one was exposed to ammonia vapour by suspending the strip in a closed beaker containing concentrated ammonia which converts FIGLU to glutamic acid; the paper was then dried at 110° for 10 min., dipped in a mixture of acetone and acetic-acid (23 : 2) to neutralise any excess ammonia, and redried at 110° for 30 sec. Both papers were finally stained with ninhydrin and 24 hours later fixed with 0·25 M. nickel sulphate. A spot appearing in the ammonia-treated strip, but not on the one treated straight with ninhydrin, and corresponding in mobility to the standard sample of FIGLU, represents this compound.

Ten normal and healthy controls, eight patients with anæmia not thought to be due to folic-acid deficiency (iron deficiency 3, pernicious anæmia in relapse 2, leukæmia 2, thalassæmia 1), and five patients with steatorrhœa were studied. All patients were given l-histidine 20 g. orally, and urine collections were made for the next 12 hours, the urine being collected in three parts; 0–5 hours, 5–6 hours, and 6–12 hours. The urine was collected with 0·5 ml. concentrated hydrochloric acid, which stabilises the FIGLU, and thymol to prevent bacterial growth.

Results

After staining the paper with ninhydrin, as little as 10 μg. FIGLU per ml. urine could be detected. Although staining with the nitroprusside-ferricyanide reagent was as sensitive as the ninhydrin method with pure samples of FIGLU it was less sensitive when urine had been added.

In three of the ten normal subjects a trace of FIGLU was observed after histidine, but none was found in the prehistidine urine sample. In four of the anæmic patients a trace of FIGLU was also found in the urine after histidine loading, none being found before, whilst in all the patients with steatorrhœa there was a marked excess of FIGLU after giving histidine, though again none was evident before. After the single loading dose of histidine excretion of FIGLU was greatest in the 5–6 hour urine sample and had usually disappeared at 18 hours.



Electrophoretogram of urines from folic-acid-deficient patients (1 = histidine; 2 = glycine; 3 = formimino-glutamic acid; 4 = glutamic acid).

E_R+F = Patient's random urine + FIGLU marker. E_R = Patient's urine alone. E_Z = Patient's urine 6 hours after 20 g. histidine orally. Upper strip has been exposed to ammonia before development with ninhydrin; lower strip has been developed with ninhydrin directly.

Only one of the patients with steatorrhœa had a megaloblastic anæmia (serum-B_{12} = 150 μ μc. per ml.); the others showed varying degrees of iron-deficiency anæmia, except one who was not anæmic. After administration of folic acid to four of these patients FIGLU did not appear after a histidine load, whilst in one patient who was given only a gluten-free diet a further test with histidine loading showed only normal amounts of FIGLU.

The figure reproduces an electrophoretogram of urine from a patient with steatorrhœa. On it have been run a random urine sample, a random urine sample containing 17 μg. FIGLU, and 25 μl. of a 5–6-hour urine sample after taking 20 g. l-histidine. The two paper strips have been stained separately, one directly with ninhydrin and the other with ninhydrin after the ammonia treatment.

From the cases so far studied it has been found simple to distinguish the folic-acid-deficient cases from the others. This has been done by diluting the urine. In the folic-acid-deficient, FIGLU can be detected even after dilution to 1 in 10, whereas in the others the FIGLU spot disappears after a 1 in 2 dilution. The excretion can be quantitated further by serial dilution of the urine to extinction of the FIGLU spot, when the maximum rate of excretion per hour is estimated. These ranged as follows:

Mr. A	600 μg. per ml.	=	72 mg. per hour (calculated over first 6–12 hrs.)
Mr. B.	800 „ „ „	=	112 „ „ „
Mr. C	300 „ „ „	=	31·8 „ „ „
Mr. D	100 „ „ „	=	5·3 „ „ „
Mrs. E	100 „ „ „	=	5·2 „ „ „
16 controls	20 „ „ „	=	0·2 „ „ „

Comment

Administration of a single loading dose of 20 g. histidine followed by the demonstration of FIGLU in the urine appears to be a very sensitive indicator of folic-acid deficiency, and is positive in patients with malabsorption syndrome before megaloblastic changes are found in the bone marrow. The use of high-voltage electrophoresis to detect FIGLU in the urine is a rapid, specific, and sensitive method and should have wide application. It seems to be so sensitive in steatorrhœa that it may even prove a useful screening procedure before proceeding to a fat balance. Positive tests have been reported in pernicious anæmia and liver disease (Carter et al. 1960), but in eighteen patients with pernicious anæmia in whom FIGLU has been measured the amounts were within normal limits (Luhby et al. 1959b). In the cases we have so far examined, the excretion of FIGLU has been so much greater in folic-acid deficiency than in other conditions that confusion should not arise. In fact we have never had to correct for variations in urine volume during the period of testing, and the analysis of a single specimen of urine passed 5–6 hours after the administration of 20 g. of histidine appears to suffice.

We are grateful to Dr. H. Waelsch for a small sample of FIGLU which we used in our initial studies.

REFERENCES

Bakerman, H. A., Silverman, M., Daft, F. S. (1951) *J. biol. Chem.* **188**, 117.
Block, R. J., Bolling, D. (1951) Amino Acid Composition of Proteins and Foods. Springfield, Ill.
Borek, B. A., Waelsch, H. (1953) *J. biol. Chem.* **205**, 459.
Carter, F. C., Schafner, G., Heller, P. (1960) *Clin. Res.* **8**, 199.
Kirby-Berry, H., Sutton, H. E., Cain, L., Berry, J. S. (1951) Texas University Publication no. **5509**, p. 22.
Luhby, A. L., Cooperman, J. M., Teller, D. N. (1959a) *Amer. J. clin. Nutr.* **7**, 397.
— — — (1959b) *Proc. Soc. exp. Biol., N.Y.* **101**, 350.
Seegmiller, J. E., Silverman, M., Tabor, H., Mehler, A. (1954) *J. Amer. chem. Soc.* **76**, 6205.
Silverman, M., Gardiner, R. C., Bakerman, H. A. (1952) *J. biol. Chem.* **188**, 117.
— — Condit, P. T. (1958) *J. nat. Cancer Inst.* **20**, 71.
Spray, G. H., Witts, L. J. (1959) *Lancet*, ii, 702.
Tabor, H., Rabinowitz, J. (1957) Biochemical Preparations, vol. v., p. 100. New York.
— Silverman, M., Mehler, A. H., Daft, F. S., Bauer, H. (1953) *J. Amer. chem. Soc.* **75**, 756.
— Wyngarden, L. (1958) *J. clin. Invest.* **37**, 824.
Westall R. G. (1960) *Biochem. J.* (in the press).

Preliminary Communication

THE INFLUENCE OF ALDOSTERONE ON MAGNESIUM METABOLISM

Mader and Iseri [1] and Milne et al.[2] found that primary aldosteronism is associated with a negative magnesium balance, sometimes with hypomagnesæmia, and that this negative balance is reversed after removal of the tumour. It is not known whether the magnesium loss is a direct effect of aldosterone, or is a consequence of the renal damage usually present.

Accordingly we have carried out full studies of the effect of aldosterone on the normal and adrenalectomised rat, using an accurate balance technique and specific flame-spectrophotometric methods.

METHODS

Animals

Female hooded rats weighing 150–170 g. were used. 48 rats were taken and divided into two main groups of 24: each group was divided into four subgroups, one subgroup serving as a control, and the other three receiving aldosterone in increasing dosage. One of the two main groups consisted of normal rats, while the other was made up of rats which had been adrenalectomised ten days previously and maintained on extra saline until the day before the experiment.

Metabolic Techniques

The rats were placed individually in metabolic cages which allowed complete separation of urine and fæces (Hanna and

1. Mader, I. J., Iseri, L. T. *Amer. J. Med.* 1955, **19**, 976.
2. Milne, M. D., Muehrcke, R. C., Aird, I. *Quart. J. Med.* 1957, **26**, 317.

EFFECTS OF ALDOSTERONE ON NORMAL AND ADRENALECTOMISED RATS

The figures for magnesium excretion are expressed as μEq. per day. The electrolyte concentrations in plasma and muscle are expressed respectively in mEq. per litre and mEq. per kg. dry fat-free solids.

—	Adrenalectomised		Normal	
	Control	Aldosterone (0·5 μg per day)	Control	Aldosterone (0·5 μg per day)
Fæcal Mg ..	112·00	260·00**	180·00	263·00*
Urine Mg ..	85·00	145·00**	109·00	139·00**
Mg balance ..	+100·00	−105·00**	+10·00	−102·00**
Muscle Mg ..	100·30	78·30**	95·80	96·10
Muscle K ..	477·00	367·00**	458·00	450·00
Muscle Ca ..	9·20	21·00**	10·30	9·50
Plasma Mg ..	1·98	1·90	1·43	1·33
Plasma K ..	7·23	4·68**	3·45	3·05*

The results were analysed by analysis of variance. The changes significant at the 1% and 5% level are indicated by ** and * respectively.

Alcock, unpublished). During the period of aldosterone administration, and for three days before this, they were given, by tube, a liquid diet identical with that described by MacIntyre and Davidsson,[3] save for the addition of chromium sesquioxide in known and constant amount. All rats received the same diet during the experiment. Extra saline was not given to the adrenalectomised animals while they were having aldosterone. Aldosterone was administered intramuscularly twice daily for three days: total daily doses were given of 0·05, 0·2, and 0·5 μg. to each animal, in each of the three treatment subgroups, within the two main experimental groups of normal and adrenalectomised rats. At the end of the experiment, the animals were anæsthetised with pentobarbitone, blood was obtained from the aorta, and muscle samples were taken from the thighs.

Statistical Methods

The results were analysed by the methods of Snedecor.[4]

3. MacIntyre, I., Davidsson, D. *Biochem. J.* 1958, **70**, 456.
4. Snedecor, G. W. Statistical Methods. Iowa State College Press, 1959.

Analytical Procedures

Electrolytes were measured in urine, fæces, and tissues by flame spectrophotometry.[3] Chromium sesquioxide was determined in fæces by the method of Smith.[5] Since chromium is completely unabsorbed, incomplete collection of fæces was unimportant and the total fæcal outputs could be calculated by expressing any substance in terms of the known daily intake of C_2rO_3.

RESULTS AND DISCUSSIONS

The detailed results are summarised in the table and the more striking changes illustrated in the figures.

It is obvious that aldosterone has a profound effect on magnesium metabolism, increasing magnesium excretion not only in the urine but also in the fæces. In the adrenalectomised group of rats in which the effects of aldosterone were in general greater, the daily fæcal excretion of magnesium on the highest dosage rose from 112 to 260 μEq., while the mean daily urine output was increased from 85 to 145 μEq. Since the dietary intake was fixed at 300 μEq. per day this increased magnesium excretion resulted in a negative balance of 105 μEq. per day (fig. 3).

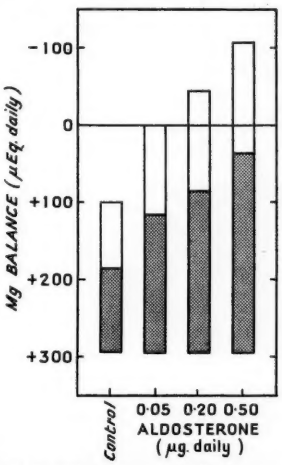


Fig. 3—The influence of aldosterone on magnesium balance in adrenalectomised rats.

The balances are charted by the method of Reifenstein et al.[6] The fæcal excretion is hatched, and the urine excretion clear.

In the adrenalectomised group, but not in the normal animals, these changes were accompanied by a depletion in muscle magnesium. This is the more striking when one considers that to produce an equivalent reduction by dietary means takes at least sixty days of depletion.[3] There was also an increase in muscle calcium and a reduction in muscle potassium, both of these changes being closely correlated with the degree of reduction of muscle magnesium (figs. 5 and 6).

MacIntyre and Davidsson [3] showed that total bone magnesium does not change in dietary magnesium depletion. Though the magnesium content of muscle did not change in our normal group, muscle still seems the likely source of the magnesium lost. Probably, in the normal animals,

5. Smith, G. F. *Analyst*, 1955, **80**, 16.
6. Reifenstein, E. C., Albright, F., Wells, S. L. *J. clin. Endocrin* 1945, **5**, 367.

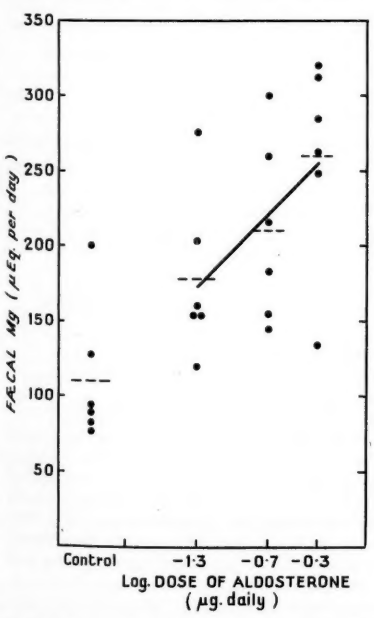


Fig. 1—The influence of aldosterone on the fæcal excretion of magnesium in adrenalectomised rats.

The line is the regression of fæcal magnesium on the log. daily dose of aldosterone (r=0·512).

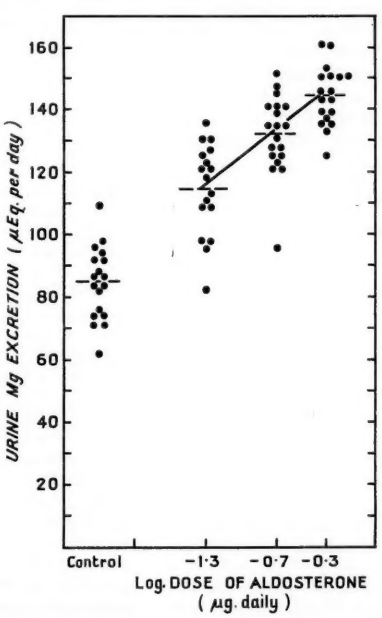


Fig. 2—The influence of aldosterone on the urinary excretion of magnesium in adrenalectomised rats.

The line is the regression of urine magnesium on log. daily dose of aldosterone (r=0·91).

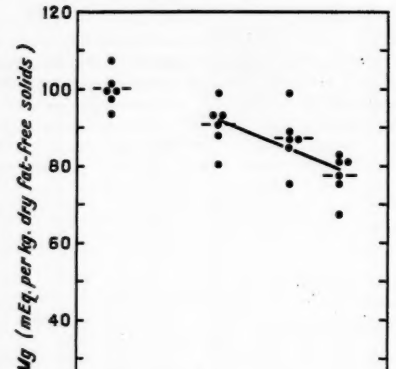


Fig. 4—The influence of aldosterone on muscle magnesium in adrenalectomised rats.

The line is the regression of muscle magnesium on log. daily dose of aldosterone ($r = -0{\cdot}632$).

other adrenal steroids modified the action of aldosterone, so that the extra magnesium excreted came from total dissolution of some of the muscle mass, but without change in the magnesium content of the remainder. Longer administration of aldosterone would probably have reduced the magnesium content of the muscle, even in the normal group. It also seems likely that, since the reduction in muscle magnesium in the adrenalectomised rats took place without a change in the plasma-magnesium level, aldosterone has a direct action on the muscle cell.

Because primary depletion of potassium from muscle does not cause secondary magnesium depletion (Cotlove et al.[7]; Alcock and MacIntyre, unpublished), although secondary potassium depletion follows magnesium deficiency,[8] the action of aldosterone on cell potassium may be at least partly secondary to its action on magnesium.

7. Cotlove, E., Holliday, M. A., Schwartz, R., Wallace, W. M. *Amer. J. Physiol.* 1951, **167**, 665.

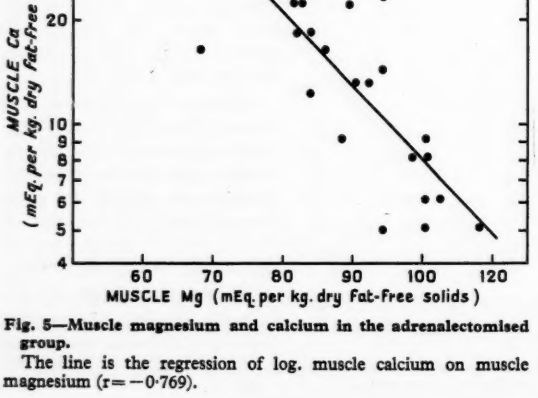


Fig. 5—Muscle magnesium and calcium in the adrenalectomised group.

The line is the regression of log. muscle calcium on muscle magnesium ($r = -0{\cdot}769$).

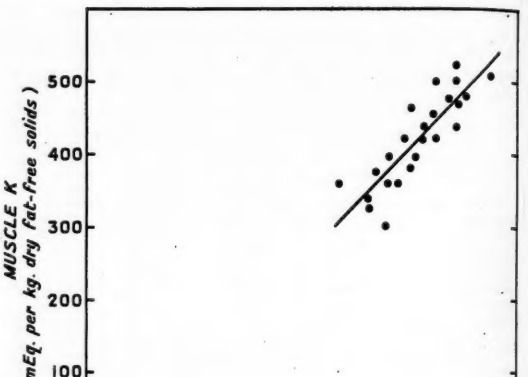


Fig. 6—Muscle magnesium and potassium in the adrenalectomised group.

The line is the regression of muscle potassium on muscle magnesium ($r = 0{\cdot}85$).

Whatever the interpretation of these findings, our results show that magnesium metabolism is profoundly influenced by aldosterone, and provide a satisfactory explanation of the magnesium depletion which occurs in primary aldosteronism.

SUMMARY

Studies in the rat showed that aldosterone profoundly affects magnesium metabolism.

In both normal and adrenalectomised animals it increased excretion of magnesium in the urine and fæces.

In the adrenalectomised, but not in the normal, animal it reduced the intracellular magnesium content of muscle.

The action of aldosterone on cell potassium may be partly secondary to a primary action on intracellular magnesium.

The magnesium depletion found in primary aldosteronism should be attributed to a direct action of aldosterone, and not to secondary renal damage.

We should like to thank Dr. A. Neher of Ciba A.-G., Basle, for the aldosterone used. It was received via the Medical Research Council Steroid Reference Collection by courtesy of Dr. W. Klyne.

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"... If a positive corrective is needed to a one-sided stress on vocational instruction or on training the intellect, what is wrong with more old-fashioned talk about the training of character and happiness? In such matters it is important to call a spade a spade rather than to spoon out social conformity from a bottle that makes it look scientifically respectable. More old-fashioned ideals like the training of intellect and of character did at least imply that children were to be treated as responsible agents worthy to carry on the activities of a civilised community; they did not imply, as does the stress on mental health, that children are to be treated as patients who have to be weaned in a kindly way to nibble at the raw meat of the modern world."—R. S. PETERS, *Listener*, July 14, 1960, p. 47.

Reviews of Books

Fundamentals of Clinical Hæmatology

BYRD S. LEAVELL, M.D., professor of internal medicine, University of Virginia School of Medicine; OSCAR A. THORUP, JR., M.D., associate professor of internal medicine, University of Virginia School of Medicine. Philadelphia and London: W. B. Saunders. 1960. Pp. 503. 70*s*.

THIS very interesting textbook shows how far the fundamentals of hæmatology have extended into the biochemical field, and how much less importance is now attached to morphology and even clinical signs and symptoms. The book does start with a brief consideration of essential morphology, but the section on the erythrocyte devotes one page to its origin and appearances and four to biochemistry, a fair knowledge of which is assumed throughout. The section on general classification deals very briefly with morphological matters and at length with the mechanisms which lead to the syndromes; this section is well up to date and includes all the latest news about hæmoglobinopathies and a discussion of primaquine sensitivity.

After general chapters, each main syndrome is considered separately. First, there is a brief look at the history, then a fairly long discussion of mechanisms, a briefer description of clinical manifestations, detailed consideration of laboratory tests, and a quick look at differential diagnosis; the course and prognosis and the treatment are shortly described, and finally there are one or two illustrative case-reports, mostly excellent. The leukæmias and the lymphomas are dealt with in one chapter each, but a separate and highly contemporary chapter on leucocytosis and leucopenia is provided and a special chapter is devoted to agents for the treatment of leukæmias and lymphomas. Lastly there is a short but effective technical section.

Remarkably forward-looking in style and arrangement, this is a very good book, notably short for one so informative. The authors hopefully address it to " the student who is being introduced to hæmatology for the first time while he is in the midst of a crowded curriculum ", and to physicians in active practice. The American medical student must have a different viewpoint from his British counterpart at present. We agree that it will be fine when students have so much background knowledge that they can start with this book, but the British student is not there yet. The book is better suited to those studying for higher examinations, and it can be warmly recommended to them—and to their teachers.

Handbook of Neurological Diagnostic Methods

FLETCHER MCDOWELL, M.D., assistant professor of medicine, Cornell University Medical College; HAROLD G. WOLFF, M.D., Anne Parriah Titzell professor of medicine, Cornell University Medical College. Baltimore: Williams & Wilkins. London: Baillière, Tindall, & Cox. 1960. Pp. 102. 36*s*.

ALTHOUGH neurological diagnosis remains primarily a matter of careful history-taking and clinical examination, there has been an increase in useful adjuvant diagnostic procedures in the past two decades. Moreover, a full clinical examination of the nervous system and particularly the examination of complex cortical function requires a more elaborate technique than is usually given in general manuals. For both these reasons a handbook devoted to neurological examination is justified. The trouble is that many of the newer diagnostic methods are so complex either in technique or in the background theory on which interpretation must be based that each requires a small volume to itself. Nevertheless it is desirable that the student and general physician should know something of these tests and their implications and limitations. This book provides such an introduction. Besides history-taking and examination which includes these aspects of cortical function, such as language, memory, and intelligence, which border on the psychiatric, the authors also discuss angiography, electroencephalography, and electromyography; and respiratory failure, an increasingly important part of neurological management, gets a brief but useful mention.

Provided the reader remembers that the information is necessarily brief and summarised, the book will prove useful to senior students and general physicians who wish to take some interest in neurological cases.

The summary at the end of the book of " minimum of essential information for understanding disease of the nervous system " is useful. A few references to sources of wider information on some special subjects would have been welcome.

Surgery and Clinical Pathology in the Tropics

CHARLES BOWESMAN, O.B.E., M.D., F.R.C.S.E., surgical specialist, Gold Coast and Ghana Governments. Edinburgh: E. & S. Livingstone. 1960. Pp. 1068. 110*s*.

AS its author indicates in a preface, this book has been compiled from notes made throughout his career. It is thus the illustrated day-to-day book of a tropical surgeon who has found interest in many surgical problems, and has the large personal experience of tropical clinical pathology acquired by the surgeon who works single-handed among primitive people. His patients are not selected before they consult him, and he is often the general practitioner. There is an interesting chapter on worms, including a description of the treatment of ascarids by intragastric insufflation of oxygen. The technique may be carried out by nurses, but the author does not mention the dangers of oxygen released from cylinders at high pressure (the gut or the diaphragm may easily be ruptured). Like most doctors in the tropics, he shows his interest in female circumcision, but he does not refer to the radical variety called " pharaonic " that prevails in spite of legal prohibition in northern Sudan. Nor does he comment on the fact of this apparently barbarous custom prevailing in the pagan black equatorial races and also among the brown Muslim Arabs further north. A milder modified form is also found among the Muslims of Egypt. The practice seems in Sudan to be a compulsion of custom but not of religion.

There is a good short chapter on bites by snakes, men, and crocodiles. Also in a chapter too short for the importance of the subject he shows the happy results of surgery for filariasis with elephantiasis. His account of the urinary disease that he has met is straightforward. Cancrum oris, the bane of undernourished children in the tropics, is well described, and the plastic repairs in vogue are noted.

This is a good book of reference for surgeons newly finding themselves in tropical countries, and they are unlikely to meet any surgical condition, including obstetric conditions, that does not receive mention. The illustrations, mostly photographs, are good, and nearly always self-explanatory.

An Introduction to Congenital Heart Disease

LEO SCHAMROTH, M.B., M.R.C.P.E., FAY SEGAL, M.D., Baragwanath Hospital and University of Witwatersrand, Johannesburg. Oxford: Blackwell Scientific Publications. 1960. Pp. 116. 22*s*. 6*d*.

THIS small book describes all common abnormalities and a few of the rarer conditions.

After an introductory chapter in which special investigations are briefly discussed, there is a chapter on the development of the heart and one on cyanosis. Each of the remaining chapters is devoted to a particular type, or group, of anatomical abnormalities. These chapters are well arranged, with clear subdivisions. The embryology, associated abnormalities, the hæmodynamics of the circulation, and clinical features are clearly set out in each case. The style is crisp and easy to read. In these respects the book is satisfactory and serves its purpose.

A few references are given to each chapter, but these seem to have been chosen so arbitrarily that they might well have been omitted. In any case, an elementary book hardly needs references to original articles.

The myth concerning the association of atrial septal defect with Marfan's syndrome has been perpetuated. In the chapter on atrial septal defect, it is rather unsatisfactory that the description should be appropriate only to simple ostium secundum without any indication that this is so, especially since the only electrocardiograph shown is very suggestive of an ostium primum type of lesion.

The illustrations are numerous, and many are simple and informative, but some of the diagrams contain inaccuracies (the relationship of the aortic arch to the pulmonary arteries is wrongly shown more than once) and others fail to show clearly what is intended, particularly the diagrams of the course of the circulation and the mixing of arterial and venous blood in the various abnormalities. In the radiographs the contrast medium is hard to identify in the angiocardiograms, and the pulmonary vascular pattern is unrecognisable in most of the straight chest films.

The paper, type, and binding are of exceptional quality for a small elementary book, and a cheaper production might commend itself to the many students who may like rather more than they are getting here for their money.

Constructive Work for Mental Health in Hong Kong

Editor: K. E. PRIESTLEY, professor of education, University of Hong Kong. London: Oxford University Press. Hong Kong: Hong Kong University Press. 1959. Pp. 108. 7*s*. 6*d*.

THIS group of lectures on problems of child mental health in Hong Kong are by a mixed group of professional, but largely non-medical, workers concerned with the subject, and they were originally delivered to a similarly composed audience. Factors such as " broken homes ", overprotection, and inconsistent and conflicting discipline seem very similar to those experienced elsewhere. There are differences, however: conflict between Oriental and Western cultures, sometimes with the persistence of the worst of both, raises problems, as do the strong economic pressures. Owing to the total lack of special schooling, educational difficulties are more prominent than they are here. Psychiatric facilities in Hong Kong are at present very meagre, but it is clear from this book that the challenge is being faced.

A Practice of General Anæsthesia for Neurosurgery

ROBERT I. W. BALLANTINE, D.A., F.F.A. R.C.S., consultant anæsthetist, St. Bartholomew's Hospital, London. With the collaboration of IAN JACKSON, D.A., consultant anæsthetist, St. Bartholomew's Hospital. London: J. & A. Churchill. 1960. Pp. 152. 27*s*. 6*d*.

THIS monograph contains information on intracranial pressure, specific cranial and spinal operations, neuroradiological investigations, and preoperative and postoperative nursing care of neurosurgical patients, besides considerable detail on anæsthetic technique. The authors are well-known supporters of spontaneous respiration for this branch of surgery, and they produce many rational arguments in its favour; but they have dealt more summarily and superficially with controlled respiration than this widespread practice deserves. So few anæsthetists, even during their period of training, have the opportunity to work in a neurosurgical unit that this work will be a most useful guide to the first occasion. It will also give them an understanding of the contribution that a good anæsthetist can make to a neurosurgical team.

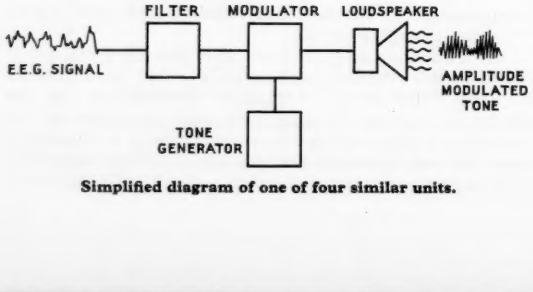
Physiology of Prematurity (Transactions of the 4th Josiah Macy Conference, 1959. New York: Josiah Macy, Jr., Foundation. 1960. Pp. 184. $4.50).—The topics occupying this distinguished symposium were heat regulation, hypothermia and asphyxia of the newborn, and chemical structure, functional integration, and renal regulation as factors in the physiology of the newborn. This book, edited by Dr. J. T. Lanman, is a verbatim report of the proceedings which is absorbingly interesting to the initiated but perhaps confusing and irritating to the non-expert. As expected, the participants speak with authority and after a wealth of experimental data; no attempt is made to be comprehensive or conclusive.

New Inventions

AUDIO-MONITORING OF ELECTROENCEPHALOGRAPHY DURING SURGERY AND ANÆSTHESIA

THE electrical activity of the brain is altered rapidly by gross changes in the cerebral blood-flow as well as by the administration of anæsthetic drugs. For several years electroencephalography (E.E.G.) has been used as a means of monitoring some of the phenomena of anæsthesia. Recent developments in cardiovascular surgery and the increasing use of hypothermia in various conditions has renewed interest in neurophysiological measurements during operations. It is known that alterations in E.E.G. patterns after a sudden dangerous circulatory disturbance commonly precede any appreciable clinical change.

Experience in the operating-theatre suggests that visual (graphic) monitoring of cerebral activity is not readily followed by anæsthetists or surgeons, whose visual concentration is usually directed elsewhere. Auditory signals of the electrical phenomena from the brain seemed to warrant investigation. Cerebral activity, as commonly recorded with E.E.G. amplifiers, shows almost constant variations in frequency and amplitude which probably correspond to a number of poorly understood events. In connection with surgical and anæsthetic procedures only some of the many changes in the patterns of the E.E.G. have known clinical importance.



Simplified diagram of one of four similar units.

Normal as well as abnormal cerebral activity recorded through the scalp is of rather low frequency, mostly below the audible range. To transform the low-frequency signals into a simplified code of audio-signals, the following method was developed which does not seem to have been previously described. Four groups, or bands, of frequency of the E.E.G. were chosen—slow, medium, fast, and very fast. Four appropriate filter units were built, into which the output of a commercial E.E.G. amplifier was fed. The output of each filter unit modulated the amplitude of a tone through either a loudspeaker or a small earphone of the hearing aid type. In addition to the visual record obtained with a pen oscillograph, it was possible to detect variations in the combination of the four tones representing different aspects of cerebral activity. By appropriate selection of the frequency bands and by adjustment in the pitch of each of the four amplitude-modulated tones, it was possible to obtain a combination of audio-signals which would change with a delay of less than one second when an alteration in cerebral activity occurred. The four modulated tones could be adjusted both in volume and pitch to the listener's auditory sensibility, or preference. It should be borne in mind that for most people harmonic relations are best avoided since they increase the difficulty of recognising sudden minor changes in tone-combination patterns. The accompanying diagram represents the general principle involved.

The electrocardiogram recorded at the same time may be fed into the apparatus together with the E.E.G., and its rhythmic characteristics are easily recognised among the less regular features of the electrical activity of the brain. Incorporation of a tape-recorder facilitates the taking of permanent records and is useful for teaching.

We wish to acknowledge a grant from the research committee of The Hospital for Sick Children, London, and the kind help of Mr. Derek Martin, of the photographic department.

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THE LANCET

LONDON 13 AUGUST 1960

Central Sterile Supply

THERE is nothing new about the idea of a hospital central sterile supply department. Twelve years ago WALTER [1] regarded such departments as essential, and a recent visitor to the United States noted that they had been introduced everywhere.[2] The first such department to be established in the United Kingdom was at Musgrave Park Hospital in Belfast,[3] and over the past two years this has been a centre of pilgrimage. Other hospitals have recently followed the lead of Musgrave Park [4–8] and further such departments are being planned with official blessing. The Minister of Health has stated (in discussing the recommendation of the Medical Research Council's Working Party on Pressure Steam Sterilisers [9] that all hospital boilers used for sterilising instruments should be replaced by pressure steam sterilisers) that " one answer to the problem may be to consider the practicability of setting up central sterile departments so as to overcome the need for having expensive items of equipment dispersed throughout hospitals ".[10] The Department of Health for Scotland has also approved the principle that new hospitals should include a central sterile supply department and that present hospitals (or hospital groups) may consider establishing such a department.

Many are opposed to centralisation in any form, equating it with paper work and bureaucracy. They will ask why the present state of affairs should be changed. The answer is not far to seek; for surveys have shown that all is not well with the sterilisation of surgical goods.[9 11–13] This suggests that supervision has been defective and could fail again when the present interest in sterilisation subsides. Another, but less direct, reason for centralisation is the introduction of the high-speed, high-vacuum, pressure-steam steriliser. This costly item can, in a working day, do the work of three to five gravity-displacement sterilisers of similar size, and at the same time will deal adequately with incorrectly packed loads which would defeat these latter instruments.[14] The high-speed high-vacuum steriliser operates automatically, thus overcoming, as much as possible, the hazard of human error. The replacement of each operating-theatre's dressing steriliser by a high-vacuum model would be intolerably expensive; so, if the full benefits of this advance are to be reaped, centralisation must be pursued. The direct benefits of centralisation are many, as the medical and nursing staffs of hospitals where it is already practised will testify. These advantages may be summarised under safety, efficiency, and economy. A chain is no stronger than its weakest link, and the longer the chain the more likely is there to be a weak link. The greater the number of people engaged in sterilisation processes, the greater is the likelihood of failure. Centralisation places all sterilisation processes under expert supervision, and thus inexperienced junior nurses no longer have to operate this potentially dangerous equipment: almost every hospital has had its serious accidents due to mishandling of sterilisers. The efficiency factor is important. A central sterile supply department can be mechanised to a degree quite impossible in individual wards and theatres; and, as the work is performed by lay staff, valuable nursing time is saved. Economy is illustrated by the reduction in the number of sterilisers needed in a hospital with central sterile supply. This represents a double saving, as not only will capital expenditure on ward boilers and theatre dressing sterilisers be avoided but the new high-speed equipment will not damage gloves and fabrics to the same extent as the old sterilisers.

It is generally accepted in this country that a central sterile supply department should process all sterile articles for use in the hospital except bedpans, unwrapped bowls and instruments for theatre use, and pharmaceuticals. Superficially this may not seem to be an unduly difficult undertaking; but in fact the introduction of central sterile supply is a major undertaking which should not be rushed into. Some schemes have been preceded by small pilot projects, such as that at Sunderland [8 15]; and all have needed much preliminary observation and planning. Fortunately the departments already functioning have a wealth of practical experience, and the Nuffield Provincial Hospitals Trust has established an experimental department at Addenbrooke's Hospital, Cambridge. Possibly future departments may be smaller than those existing in the United States or this country, owing to the introduction commercially of pre-packaged sterile goods [2]; and certainly the increasing use of disposable products will lessen the work of the department.

Two important questions should be faced early in the planning stage. The first concerns site and extent. Most present departments are situated in the hospital which they serve, but some are planned to be situated some distance away because of lack of space at the hospital or (as in the Wessex hospital region [16]) because the whole region is to be served (in this case by two centres). From what is happening in Wessex and from what the Army has accomplished at Aldershot [17] it is obvious that a central sterile supply department can cover a large hospital group or a region, and extensions to cover smaller hospitals in the area may be possible. Group coverage of this sort is well established in laundry work, and there is much to be said for siting a group central

1. Walter, C. W. The Aseptic Treatment of Wounds. New York, 1948.
2. Davies, J. O. F. *Brit. med. J.* 1960, i, 1879.
3. Stott, F. T. *Nursing Times*, 1960, **56**, 41.
4. *ibid.* p. 541.
5. Johnston, H. P. *Nursing Mirror*, June 3, 1960, p. v.
6. Seely, M. A. *Nursing Times*, 1960, **56**, 717.
7. *ibid.* p. 757.
8. Thompson, M. E. *ibid.* p. 869.
9. *Lancet*, 1959, i, 425.
10. H.M. (59) 33, see *Lancet*, 1959, i, 791.
11. Bowie, J. H. *Pharm. J.* 1955, **174**, 473.
12. Howie, J. W., Timbury, M. C. *Lancet*, 1956, ii, 669.
13. Present Sterilising Practice in Six Hospitals. Nuffield Provincial Hospital Trust. London, 1958. See *Lancet*, 1958, ii, 1359.
14. Knox, R., Penikett, E. J. K. *Brit. med. J.* 1958, i, 680.
15. See *Lancet*, 1960, i, 661.
16. *ibid.* p. 986.
17. Army Medical Directorate, Bulletin no. 12, 1960.

sterile supply department near the group laundry. The second important point is the relation of the department to the hospital administration. A central sterile supply department should be accorded the same degree of autonomy as the pharmacy, and the supervisor should be of suitable professional status. Most departments are supervised by a senior male or female nurse. Such a choice is rational, and is regarded as essential by most members of the nursing profession. But at a recent symposium on sterilisation procedures [18] members of other professions argued that the pharmacist, with his training in sterilisation processes and microbiology, was the most suitable supervisor.

Among recent descriptions of central supply services the most detailed is that published by the Army.[17] A successful pilot scheme covered 675 main hospital beds plus six camp hospitals and forty-nine medical and welfare centres in the Aldershot district. This scheme was operated by a warrant officer, a sergeant, and up to six other ranks. This publication, together with the various articles which have appeared in the nursing journals and elsewhere [1 3–8 19] provides much useful information for those planning a central sterile supply department; but the best way to learn, as always, is by practical experiment.

Testing a Measles Vaccine

THERE has been rapid and encouraging progress in the search for a vaccine against measles, and investigation from two quite different directions is converging on a single point.

The first line of research started six years ago when ENDERS and PEEBLES [20] showed that measles virus could be grown in tissue cultures of human or monkey kidney cells. Next it was found that the Edmonston strain of measles virus, after numerous passages in cultures of human tissues in vitro, could be adapted to grow in cultures of chick-embryo tissues.[21] The chick-embryo-adapted virus was shown to have diminished pathogenicity for monkeys and man (much as the chick-embryo-adapted 17D strain of yellow-fever virus was shown twenty years earlier to have diminished pathogenicity); and KATZ and ENDERS [22] have reported the effects of inoculating children with the modified measles virus. The virus was given by subcutaneous inoculation to 11 children. All showed mild pyrexia or rash, or both, six to ten days after inoculation; but in no case did the inoculation lead to any discomfort or change in the children's routine activities. No virus was recovered from the throat or the blood of these children, and susceptible children in contact with the inoculated children did not become infected.

Further results of the same kind have now been reported by HOEKENGA et al.,[23] who studied measles in Panama. In that area measles is endemic and every few years becomes epidemic, severely affecting labourers and their families on the banana plantations. In March, 1959, a susceptible population of Indians came with their families from relatively isolated areas to work on the farms. Many cases occurred in small children, and some in older children and young adults. 1611 people under 30 years of age with no history of measles were selected for a trial of measles vaccine; about half volunteered to be vaccinated, and the remainder were used as controls. Over 400 were vaccinated with the Edmonston strain of measles virus. In children under 5 years old, reactions were common. About 70–80% of them had fever on the sixth to eighth day; this was usually mild, but the rectal temperature occasionally reached 105°F. In half of them a macular rash developed and lasted one to four days. Older children or adults showed no reaction to the vaccine, and at all ages satisfactory antibody responses to measles virus developed. In the ensuing four and a half months 3 out of 453 vaccinated children contracted measles, compared with 32 of 356 controls.

Recently, too, SMORODINTSEV et al.[24] in Leningrad have tested a strain of measles virus ("Leningrad 4F") which they had adapted to grow in chick-embryo tissue cultures. The virus was inoculated intradermally or subcutaneously in 113 children aged 2–6 years. The majority of the children had a mild febrile reaction with a slight rash but without any disturbance in their appetite, sleep, or general condition—a reaction very similar to those reported by KATZ and ENDERS and by HOEKENGA et al. The Leningrad workers also observed that the modified measles they induced with their vaccine was non-contagious and that it induced a good antibody response in about 80% of the children, along with resistance to a second inoculation in a few children who had responded to the first inoculation.

The second approach originated in 1945 with an observation by PINKERTON et al.[25] that the pathological pictures of measles and distemper were strikingly alike: in both infections there were characteristic cytoplasmic and nuclear inclusions in epithelial tissues and numerous multinucleated giant cells. Subsequently, ADAMS and IMAGAWA [26] pointed to an antigenic relationship between measles and distemper viruses in in-vitro experiments. The degree of antigenic relationship between these viruses is undecided; but KEMPE [27] inoculated 15 children with live distemper without producing any ill effects and showed that 3 of them resisted challenge with the Edmonston strain of measles virus. Now, HOEKENGA et al.[23] have tested distemper vaccine in Panama at the same time as the measles vaccine. The distemper vaccine caused no reactions, and in the following four and a half months 14 of 388 vaccinated individuals, compared with 25 of 414 controls, contracted measles.

The results with distemper vaccine are not too hopeful, but the trials with measles vaccine seem to be giving very encouraging results. At the moment it is not known how long after vaccination resistance to natural infection

18. The Operation of Sterilising Autoclaves. Pharmaceutical Press, London, 1959.
19. Perkins, J. J. Principles and Methods of Sterilisation. Springfield, Ill., 1956.
20. Enders, J. F., Peebles, T. C. *Proc. Soc. exp. Biol., N.Y.* 1954, **86**, 277.
21. Katz, S. L., Milovanovic, M. V., Enders, J. F. *ibid.* 1958, **97**, 23.
22. Katz, S. L., Enders, J. F. *A.M.A. J. Dis. Child.* 1959, **85**, 605.
23. Hoekenga, M. T., Schwarz, A. J. F., Palma, H. C., Boyer, P. A. *J. Amer. med. Ass.* 1960, **173**, 868.
24. Smorodintsev, A. A., Boichuk, L. M., Shikina, E. S., Batanova, T. B., Bystryakova, L. V., Peradze, T. V. *Acta virol.* 1960, **4**. 201.
25. Pinkerton, H., Smiley, W. L., Anderson, W. A. D. *Amer. J. Path.* 1945, **21**, 2.
26. Adams, J. W., Imagawa, D. T. *Proc. Soc. exp. Biol., N.Y.* 1957, **96**, 240.
27. Kempe, C. H. Cited by S. L. Katz and J. F. Enders (footnote 22).

persists; nor is it known whether further attenuation of the virus, which might be expected to reduce the number of reactions to vaccination, would also reduce the immunogenic power of the vaccine. The fact that no cases of contact infection from the vaccinated have so far been detected will help to commend this vaccine to public-health authorities. Certainly measles is a very serious problem in isolated communities. In the epidemic in Greenland in 1951 [28] there was a 99·9% morbidity among 4320 persons and a mortality-rate of 1·8%; and complications occurred in 45%. Figures such as these make us realise that the painstaking attention which is being given to this disease is amply justified.

Argentaffinoma and Bronchial Adenoma

SOME bronchial adenomas—the so-called " carcinoid " type—look histologically rather like some argentaffinomas, but they are not argentaffin (that is to say, they do not blacken spontaneously in silver solutions) and the resemblance has usually been dismissed as superficial. WILLIS,[29] for instance, does not mention the " carcinoid " variety in this connection. But it appears now that the resemblance is no accident: there are two kinds of bronchial adenoma, and one is very closely related to argentaffinoma.

Six cases have now been described in which metastasising bronchial adenomas have been associated with the characteristic clinical (flushing, diarrhoea, &c.) and biochemical (raised blood-5-hydroxytryptamine and raised urinary 5-hydroxy-indole acetic acid) picture of argentaffinomatosis. It was possible to ascribe the earlier reports to failure to identify the primary neoplasm, but two cases [30 31] have now been described in which a full and careful necropsy left no serious doubt that the bronchial tumour was the real primary. Moreover, it seems that the lack of true argentaffin reaction in bronchial adenomas has been accepted too easily. WILLIAMS and AZZOPARDI [31] report that a thorough search of nine carcinoid bronchial adenomas revealed that, in no fewer than four cases, at least a few cells gave either diazo or argentaffin reactions (usually both); including the less specific but still highly significant argyrophil reaction and fluorescence under ultraviolet light, only one of the nine showed no evidence whatever of histochemical affinity with argentaffinoma. Certainly in most ileal and appendicular carcinoids the histochemical reactions are much more striking than in any of the bronchial tumours so far described, but some ileal tumours giving rise to the argentaffinomatosis syndrome in its most florid and characteristic form [32] have been altogether devoid of characteristic histochemistry. We must apparently take it as proved that physiologically active tumours secreting 5-hydroxytryptamine (5-H.T.) can arise from the bronchus.

Some interesting corollaries follow from this. In the first place it can probably be assumed that some cells normally present in the bronchial glands secrete 5-H.T. Here one runs into the exceedingly difficult subject of the argyrophil cells. Ileal and appendicular argentaffinomas are known to be related to argentaffin cells, which are normally present at these sites. Elsewhere in the gut argentaffinomas are related to argyrophil cells, giving a far less specific reaction, but probably also capable of secreting 5-H.T., and presumably the source of argentaffinomas that arise in such sites as the stomach and colon. These argyrophil cells present many difficult problems [33]: according to some accounts they are exceedingly widely distributed, and, though some of the cells which give the reaction (e.g., the β cells of the pancreas) are probably not to be included in the same category, they may represent an unexpectedly generalised system of 5-H.T.-secreting epithelial cells—possibly, as MASSON suggested, of neural crest origin. WILLIAMS and AZZOPARDI suggest that the argentaffin reaction depends not so much on the ability of the cell to secrete 5-H.T. (or, as we once suggested, 5-hydroxy-tryptophan [34]) as on the presence in the cell of a protein capable of combining reversibly with the amine to form granular aggregates as a means of storage.

WILLIAMS and AZZOPARDI further complicate the matter by describing a case of what seemed to be a typical enough oat-cell carcinoma of the bronchus actively secreting 5-H.T. in large amounts. If this is accepted (and the evidence seems good) it suggests that we must re-examine the nature of oat-cell carcinoma. Clinically and epidemiologically oat-cell carcinoma has such obvious affinities with squamous carcinoma of the bronchus that it has come to be regarded very much as an anaplastic variant of the latter. KREYBERG's data,[35] for instance, show that oat-cell and squamous carcinoma have nearly parallel incidences in different populations and are both closely related to cigarette consumption—contrasting sharply in this respect with bronchial adenocarcinoma, whose level varies little with place, race, time, or sex. Yet BARNARD's [36] classical demonstration that " mediastinal sarcomas " were carcinomas of the bronchi depended very largely on the finding of adenocarcinoma-like areas in them; and AZZOPARDI [37] has reminded us how common they are. These areas, however, do not really resemble the true bronchial adenocarcinoma: if anything, they look most like the cylindromatous variety of bronchial adenoma, the variety which does *not* secrete 5-H.T. Nothing perhaps is certain except that we have been oversimplifying the position: there is more than one genuinely distinct kind of bronchial carcinoma as well as of bronchial adenoma. Possibly the " carcinoid " bronchial adenoma and the oat-cell carcinoma have affinities greater than we have suspected, but the idea is full of difficulties.

This is not the first time that it has been suggested that there is more than one kind of bronchial adenoma. Attempts to prove this, based on purely histological

28. See *Lancet*, 1953, i, 780.
29. Willis, R. A. Pathology of Tumours; p. 376. London, 1953.
30. Warner, R. R. P., Southern, A. L. *Amer. J. Med.* 1958, **24**, 903.
31. Williams, E. D., Azzopardi, J. G. *Thorax*, 1960, **15**, 30.
32. Smith, A. N., Nohus, L. M., Dalgliesh, C. E., Dutton, R. W., Lennox, B., Macfarlane, P. S. *Scot. med. J.* 1957 **2**, 24.
33. Campbell, A. C. P. *in* Modern Trends in Pathology (edited by D. H. Collins): p. 231. London, 1959.
34. *Lancet*, 1957, i, 725.
35. Kreyberg, L. *Brit. J. Cancer*, 1955, **9**, 495. Doll, R., Hill, A. B., Kreyberg, L. *ibid.* 1957, **11**, 43.
36. Barnard, W. G. *J. Path. Bact.* 1926, **29**, 241.
37. Azzopardi, J. G. *ibid.* 1959, **78**, 513.

studies, have not met with much success. Now a new and independent line of inquiry has recently led to very similar results. Dr. R. G. J. WILLIGHAGEN, of Leiden, reported in May to a joint meeting of the Dutch and British Pathological Societies in Utrecht a survey of the enzyme patterns of a large number of tumours, in which he used histochemical methods on cryostat sections of biopsy material—a method of great potential value which is just beginning to produce useful results. His six bronchial adenomas fell neatly into two groups with strikingly different enzyme patterns, corresponding to the carcinoid and cylindromatous histological types. The difference consisted in the presence of the enzymes 5-nucleotidase, adenosinetriphosphatase, and esterase in the carcinoid tumours. There is no hint here of any direct association of these enzymes with synthesis of 5-H.T., though they may indicate a higher level of metabolic activity. Unfortunately, no histochemical methods exist for the tryptophan 5-hydroxylase and the 5-hydroxy tryptophan decarboxylase involved in the production of 5-H.T.: such methods might revolutionise this whole subject.

Annotations

ONE FORCES' MEDICAL SERVICE?

ANOTHER round in the debate on unification of the medical services of the Armed Forces opened last year when the Select Committee on Estimates declared themselves in favour of pooling the resources of the three medical branches.[1] The committee were not convinced that the establishment of a common organisation need be prevented by the specialised needs of each Service, and they criticised the Service Departments as " disappointingly inflexible " in their attitude to this proposed reform. The latest observations of the Ministers concerned, published [2] last week, will do little to alter the committee's view.

Much has already been achieved in the way of integration between the three branches, and the Ministers by no means suggest that this process has reached its limit; but, they declare, the scope for improving efficiency or saving money is less in inter-Service cooperation than in detailed improvements and economies in the individual services. The first priority must be " ensuring vigorous, fast-moving, and imaginative administration " of the three medical arms; for " the quality of each Service's medical administration can affect costs and efficiency to a very material degree " and " by contrast, the benefits obtainable from further inter-Service co-ordination are at best marginal ". This is the decided view of the four Departments (including the Ministry of Defence) and they sound as though they are prepared to stick to it.

After this general broadside, the Ministers go on to tackle the committee's recommendations in detail. In doing so they are often able to explain what has already been done in the direction the committee are pointing, but they are seldom prepared to go all the way. For example, the Medical Services Coordinating Committee received quite a beating from the Select Committee, who took " a serious view " of its shortcomings and said it should be replaced by a new and enlarged coordinating committee, similar to that proposed by the Waverley Committee. But the Ministers will not have this because " the administration of the medical services, as of other services, is a normal and direct responsibility of Service Ministers, which must be carried out by persons under their direct authority ". This severity is softened a little by the proposal to establish a small panel of civilian professional advisers, who will, when needed, advise the Medical Services Coordinating Committee.

Both sides in this round of the argument seem to be operating from securely entrenched positions; but if, as the Select Committee recommend, there is an early debate in the House on this matter, then some of the stagnation of trench conflict will be avoided.

1. Fourth Report from the Select Committee on Estimates. Session 1958–59. Medical Services of the Armed Forces. H.M. Stationery Office, 1959. See *Lancet*, 1959, ii, 336.
2. Sixth Special Report from the Select Committee on Estimates. Session 1959–60. Medical Services of the Armed Forces. H.M. Stationery Office. Pp. 12. 9*d*.

PHENYLKETONURIA

PHENYLKETONURIA was the first of the hereditary types of mental defect to be studied in terms of its fundamental biochemical lesion—an inability to convert phenylalanine to tyrosine [1] because of the absence of a labile hepatic fraction of the hydroxylating enzyme.[2 3] Even though the relationship between biochemical disturbance and mental defect remains obscure, mounting evidence indicates that restriction of phenylalanine intake [4] will allow the brain to develop normally. This preventive aspect has probably been largely responsible for much of the recent interest, both scientific and lay, in what is admittedly a rare disease. At a recent conference in London on the scientific study of mental deficiency, held in connection with World Mental Health Year, a whole session was devoted to a discussion of its various facets.

In the past, biochemical management has proved difficult because there was no completely satisfactory rapid method for assay of serum-phenylalanine levels. Although experts differ, the majority view is that urine phenylpyruvic-acid assay alone is unreliable as a yardstick of treatment. A recently described method of enzymatic spectrophotometry for serum-phenylalanine [5] will probably be of great help here. Some of the difficulties encountered during five years' experience of treatment by restricting phenylalanine intake [6] were recounted at the conference by Prof. J. R. Squire who, although convinced of its efficacy, emphasised the importance of early diagnosis if treatment is to be successful. Ideally urine testing should be performed at two and six weeks (excretion of phenylpyruvic acid begins at a variable interval after birth in affected patients) but one test at three weeks is probably a fair compromise.

Whilst the evidence in favour of the dietary regime is highly suggestive,[7] it is not completely watertight and many workers would feel happier if a controlled clinical trial were performed. Thus, a small proportion of phenylketonurics do not develop the mental defect,[8–12] and, again, the reason for this is unknown. Dr. H. A. Waisman

1. Jervis, G. A. *J. biol. Chem.* 1947, **169**, 651.
2. Wallace, H. W., Moldave, K., Meister, A. *Proc. Soc. exp. Biol., N.Y.* 1957, **94**, 632.
3. Mitoma, C., Auld, R. M., Udenfriend, S. *ibid.* p. 634.
4. Bickel, H., Gerrard, J., Hickmans, E. M. *Lancet*, 1953, ii, 812.
5. La Du, B. N., Michael, P. J. *J. Lab. clin. Med.* 1960, **55**, 491.
6. Blainey, J. D., Gulliford, R. *Arch. Dis. Childh.* 1956, **31**, 452.
7. Knox, W. E. *Pediatrics*, 1960, **26**, 1.
8. Cowie, V. A. *Lancet*, 1951, i, 272.
9. Cowie, V., Brandon, M. W. G. *J. ment. def. Res.* 1958, **2**, 55.
10. Low, N. L., Armstrong, M. D., Carlisle, J. W. *Lancet*, 1956, ii, 917.
11. Coates, S., Norman, A. P., Woolf, L. I. *Arch. Dis. Childh.* 1957, **32**, 313.
12. Hsia, D. Y.-Y., Knox, W. E., Paine, R. S. *J. Dis. Child.* 1957, **94**, 33.

and his team [13] have recently been successful in producing experimental phenylketonuria in the rat and their preparation may shed light on problems such as this.

Another outstanding question was discussed at the conference by Dr. Merton Sandler, who, with his colleagues, demonstrated a decreased 5-hydroxyindole production in phenylketonuria.[14 15] As 5-hydroxytryptamine probably has a role in normal brain function,[16] it is tempting to speculate that the disturbance in 5-hydroxyindole metabolism is connected, directly or indirectly, with the mental defect. This biochemical upset, which has been confirmed clinically by two independent groups,[17 18] and also experimentally on the Waisman preparation by Dr. Y.-Y. Hsia, probably stems from some degree of inhibition of 5-hydroxytryptophan decarboxylase,[19 20] by aromatic-acid metabolites of phenylalanine which are produced in abnormally high concentration in phenylketonuria. Dr. Sandler drew attention to a chance observation in the course of this work which may have far-reaching implications. Many of the non-phenylketonuric mental defectives investigated as control groups were found to have a very high 5-hydroxyindole production when compared with normal subjects.[21] This seemed to be independent of such factors as physical handicap and, indeed, could be correlated only with a gross degree of mental defect. A disturbed 5-hydroxyindole metabolism is, then, a feature of both phenylketonuric and certain groups of non-phenylketonuric mental defectives. But we are gradually gaining perspective in these problems and it is likely that other biologically active amines, of importance in the central nervous system, are also involved.

RESPONSE TO TREATMENT OF CHRONIC CARDIAC FAILURE

MANY studies have been made of the hæmodynamic disturbances in congestive heart-failure. Selzer and McCaughey [22] have now investigated cardiac function in patients in whom heart-failure had been brought under control by medical treatment. 50 patients with disease of the left ventricle were studied. In the majority ischæmic heart-disease and hypertension were the underlying disorders; but a minority had aortic-valve disease, and 3 had "idiopathic myocarditis". The patients were studied by cardiac catheterisation when symptoms and signs of cardiac failure had disappeared and a full response to diuretics had been obtained.

The circulatory abnormalities fell broadly into two categories. In one, the indirect left atrial pressure (pulmonary capillary venous "wedge" pressure) was normal at rest, indicating a normal left ventricular end-diastolic filling pressure; while in the other the indirect left atrial pressure at rest was persistently raised, suggesting persistence of left ventricular failure. Where the left atrial pressure was normal the cardiac output was either normal (judged by an arteriovenous difference of less than 5·5 vol. %) or reduced. When the output was normal the pulmonary arterial and right atrial pressures were usually also normal or nearly normal; but when the output was low the pulmonary vascular resistance was unusually high. The response to exercise was almost always abnormal, the pulmonary arterial pressure rising without a commensurate rise in output—indicating an increase in pulmonary vascular resistance with effort.

The patients with a persistently raised left atrial pressure after treatment were regarded as having chronic left ventricular failure. In some of them the cardiac output was normal or close to normal, and mild passive pulmonary arterial hypertension was present, pulmonary vascular resistance being normal. But in others the pulmonary vascular resistance was raised, sometimes grossly, and in such cases increased right atrial pressure suggested right in addition to left ventricular failure. In all 50 cases the cardiac output was inversely related to pulmonary vascular resistance, and when the latter exceeded 300 dynes/sec./cm.$^{-5}$ (3·7 units), the cardiac index was less than 2·5 l./min./m.^{2}[23]

Selzer and McCaughey conclude that failure of the left ventricle responds to therapy in three ways: first, the cardiac output, the ventricular filling pressure, and therefore the left atrial pressure, return to normal at rest, but the response to exercise remains abnormal indicating impaired functional reserve; secondly, the ventricular filling pressure returns to normal at rest but the cardiac output remains low; thirdly, the resting cardiac output returns to normal but the left ventricular filling pressure and left atrial pressure remain raised at rest. In this third group the pulmonary vascular resistance rises and may contribute to right ventricular failure and tricuspid insufficiency, which tend further to reduce the cardiac output. Probably the left atrial and pulmonary venous hypertension are followed by pulmonary arteriolar vasoconstriction, as has been postulated in mitral stenosis.[23 24] In the cases studied the nature and severity of the hæmodynamic disturbances were unrelated to the ætiology, duration of symptoms, and severity of cardiac failure; and, as might be expected, many patients with satisfactory clinical recovery from failure, and with little disability, had severe hæmodynamic abnormalities.

These findings suggest that restriction of effort, cardiotonic drugs, and possibly diuretics should be continued after apparently full clinical recovery; for the myocardium requires additional support to cope with the extra work entailed by physical exertion. The importance of effectively reducing left ventricular end-diastolic pressure by adequate treatment is obvious for this will prevent an increase in pulmonary venous pressure, pulmonary œdema, and pulmonary arteriolar constriction, with reduced cardiac output and eventually right ventricular failure. Digitalis, by its stimulant action on the ventricular myocardium, has been shown to improve myocardial function and reduce left ventricular filling pressure. Consequently left atrial and pulmonary venous pressures fall, and the raised pulmonary vascular resistance is reduced, so that the cardiac output increases.[25 26] It is clear from this work that digitalis should be continued after clinical recovery from left ventricular failure in sinus rhythm; and it is worth remembering that theophylline ethylene

13. Waisman, H. A., Wang, H. L., Harlow, H., Sponholz, R. R. *Proc. Soc. exp. Biol., N.Y.* 1959, **101**, 864.
14. Pare, C. M. B., Sandler, M., Stacey, R. S. *Lancet*, 1957, **i**, 551.
15. Pare, C. M. B., Sandler, M., Stacey, R. S. *Arch. Dis. Childh.* 1959, **34**, 422.
16. Gaddum, J. H. *Proc. XXth int. Congr. Physiol.* 1956, **1**, 442.
17. Berendes, H., Anderson, J. A., Ziegler, M. R., Ruttenberg, D. *J. Dis. Child.* 1958, **96**, 430.
18. Baldridge, R. C., Borofsky, L., Baird, H., Reichle, F., Bullock, D. *Proc. Soc. exp. Biol., N.Y.* 1959, **100**, 529.
19. Davison, A. N., Sandler, M. *Nature, Lond.* 1958, **181**, 186.
20. Pare, C. M. B., Sandler, M., Stacey, R. S. *Lancet*, 1958, **ii**, 1099.
21. Pare, C. M. B., Sandler, M., Stacey, R. S. *J. Neurol. Neurosurg. Psychiat.* 1960 (in the press).
22. Selzer, A., McCaughey, D. J. *Amer. J. Med.* 1960, **28**, 337.
23. Wade, E. G., MacKinnon, J., Vickers, C. H. F. *Brit. Heart J.* 1956, **18**, 458.
24. Goodwin, J. F. *Brit. J. Radiol.* 1958, **31**, 174.
25. Harvey, R. M., Ferrer, M. I., Cathcart, R. T., Richards, D. W., Cournand, A. *Amer. J. Med.* 1949, **7**, 439.
26. Bayliss, R. I. S., Etheridge, M. J., Hyman, A. L., Kelly H. G., McMichael, J., Read, E. A. S. *Brit. Heart J.* 1950, **12**, 317.

diamine (which can be given in suppository form, or by mouth as choline theophyllinate) may also be of value in improving myocardial function.[27]

THE SCHOOL DENTAL SERVICE

IN this country, only 2% of children leave school dentally fit, and one-third of the adult population wear dentures.[28] During the past decade much more has been learnt about the ætiology of dental caries, and of the influence of different types of diet, especially those containing large amounts of sugar and refined carbohydrates. As Parfitt [29] said recently, however, " dental decay among children is probably the only thing apart from lung cancer that is steadily winning the battle against modern science ".

Two things aggravate the situation: the public apathy towards matters of dental health (one-third of the population never visit the dentist [28]), and the failure of recruitment to the profession to keep pace with retirements. These two factors are to some extent interdependent, since a decreasing and ageing dental profession, however willing, cannot carry out dental-health propaganda on a sufficiently large scale, and 35% of the school dental officers in this country are over 55. The present position is that there are more aspirants to dentistry than there are places in the dental schools. Plans have been made to enlarge existing schools and to build new ones, but years must elapse before these measures can have much effect on the number of dental surgeons in practice. Even if more dentists were available it is unlikely that the school dental service—a vital part of any scheme for better dental health—would derive much benefit.

We have heard much—perhaps too much—of the large incomes earned by dental surgeons in the National Health Service. In 1959, 17 single-handed dental surgeons were able to earn between £15,000 and £20,000 a year,[30] and there are many, like Professor Aitchison,[31] who believe that such incomes are not possible if treatment is honestly and conscientiously carried out. MacGregor [32] considers that the present system of itemised payment for treatment lays itself open to abuse by the less scrupulous members of the profession. But it is often forgotten that many strictly ethical dental surgeons in the National Health Service earn far more than a school dental officer, whose income, unless he is fortunate enough to be a senior dental officer in a large area, is limited to less than £2000 a year.

In his presidential address to the British Dental Association, Mr. Duncan MacGregor [33] declared that the dental welfare and treatment of children is a " national scandal ", and condemned many local authorities for failing in their duty to the children in their care. The provision for dental treatment is less adequate than it was ten years ago. For an efficient school service, able to make annual school inspections and able to provide full and prompt treatment, it is usually reckoned that 1 dental officer is needed for every 3000 children. At present the number varies from 1 for 4000 in a few areas to 1 for 14,000 in less attractive parts of the country. In 1955, the national average was 1 for 6760, and now it is undoubtedly even lower.[34] In London the ratio is 1 full-time dental officer to 6900 children.

As MacGregor points out, no really effective steps have been taken to deal with an ever-worsening situation. The Government scheme for training 60 dental ancillaries every two years, although a move (and a controversial one) in the right direction, can be no more than a token offering at present. In New Zealand, with a child population of about 500,000, it took many years to train enough ancillaries—and in this country there are about 8 million children to be cared for. MacGregor suggests that part of the large sums of money now expended on a comprehensive dental service should be diverted to the school dental service to provide more generous salaries in order, as he says, to " attract, or even bribe, more young men and women to take up this work as a career of which they could be proud ". More funds are needed, too, for the support of national dental-health campaigns. Any increase in the number of school dental officers would probably detract from the standard of service to the adult population. But an efficient school service would inevitably and fairly quickly reduce the demands made upon the National Health Service—and decrease the number of adult " dental cripples ".

THE CONGO

As we reported last week, the World Health Organisation has set up an office in Leopoldville, whose main function will be to make the best possible use of all the international medical teams sent to the Congo. Dr. M. G. Candau, director-general of W.H.O., has been in Leopoldville for a few days, and is represented in the new republic by Dr. Prince M. Kaul, an assistant director-general. Dr. J. McKenzie Pollock, of the U.N. services for Palestine refugees, is in charge of the Leopoldville office, with Dr. F. A. Soliman and Mr. Brian Edwards. Dr. Athemas Bellerive, formerly director-general of the Haiti Ministry of Health and now public-health administrator in the W.H.O. regional office for South-East Asia, is acting as adviser to the Congo's Minister of Health. Among the special W.H.O. advisers now in the Congo are Dr. Thomas Evans, Dr. Arne Barkhuus, Dr. Simon Btesh (formerly director-general of the Ministry of Health, Israel), and Dr. A. Mochi and Dr. V. Zammit-Tabona, two W.H.O. administrators who have gone to the Kasai province to plan emergency medical services. A 16-man Israeli team arrived on July 26, and a team of 20 was offered by Ghana. Dr. Candau has gratefully acknowledged the great assistance given by national Red Cross societies.

In a letter to the Royal Society of Tropical Medicine and Hygiene, Dr. David Wilson says that the republic has fewer than 200 doctors for 14 million people. With two other medical missionaries evacuated to Leopoldville, he is " trying to cope with the emergency surgery and obstetrics in the large central hospital ". The Protestant missionary doctors have set up a Congo Medical Relief Centre (postal address: B.P. 123, Léopoldville, République du Congo) and are appealing for gifts of money, medicines, and hospital supplies. Dr. Wilson adds: " We would be delighted to hear of any doctors who might be able to come and give us some help, even for a few weeks."

We regret to record the death, on Aug. 8, of Dr. GARFIELD HODDER WILLIAMS, who since 1927 has been a member of the board of directors of this journal.

27. McMichael, J. Pharmacology of the Failing Human Heart. London, 1950.
28. Jackson, G. Quoted in *Pharmaceutical J.* March 26, 1960.
29. Parfitt, N. *Guardian*, April 11, 1960.
30. Written Parliamentary answer on behalf of the Ministry of Health July 26, 1960.
31. Aitchison, J. *Scotsman*, July 19, 1960
32. MacGregor, D. *ibid.*
33. MacGregor, D. *Brit. dent. J.* 1960, **109**, 49.
34. Mason, D. E. *Nat. Parent-Teachers Bull.* 1960, **1**, 5.

Points of View

DOCTORS, ADMINISTRATORS, AND THERAPEUTIC COMMUNITIES

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THE Mental Health Act of 1959 allows of change both in general and in mental hospitals but does not always compel it. It may be useful, therefore, to survey some of the basic concepts which can be used for guidance.

As a general rule, in all medical work the ill patient is also anxious, and this is one of the main factors on which his relationship with the doctor is based. What is sought from the doctor is often a mixture of omniscience and omnipotence; and the patient or relative seizes on many different things, depending on his own personality, to enhance the status of the doctor. The process may range from trivial observations of a highly personal kind to sober appraisal of qualifications and professional experience; but it usually includes much unconscious projection on the part of the patient. The doctor may prefer not to fill such a role, and indeed may take steps to limit it. But he must still allow for the patient's needs, and, since the projection is by the patient, he may not have much direct control of the situation.

Exactly how important this emotional element in treatment will be cannot be known beforehand. But it is always there, and can never be safely passed over, unless sometimes in emergencies. An adequate medical service can only be provided, therefore, if the demands of the doctor-patient relationship are accepted as a necessary, though often implicit, part of medical treatment. It is this which gives a special character to administrative work in medicine, and the administrative machine requires to be organised in such a way that it is governed by these subtle human relationships, which provide a considerable part of its raison-d'être.

When the patient attends a hospital, non-medical members of the staff to some extent represent the doctor. They therefore play the role of therapist in some part. Whoever has to do with the patient at any given moment thus becomes the most important immediate clinical figure.

Amongst the hospital medical staff, similarly, clinical authority resides in that doctor who is in immediate touch with the patient, and this applies no matter how junior the doctor. Thus the senior in a clinical team may often have to defer to a junior, even though temporarily, over a particular point, if the relationship with the patient, and so the treatment situation, is not to be disturbed.

Some senior clinicians themselves do not always understand this. As Fox [1] observes, "In a hierarchy where everyone is clearly labelled and wears a uniform it is difficult for the bishop to believe that he may be less valuable than the parish priest." It is not surprising, therefore, that some administrators fail to understand. The common view of administration is that authority emanates and controls from above downwards, and that a doctor, as an employee of a regional board, or the Ministry, for example, carries out duties entrusted to him. It is considered that he is supervised and guided; his seniors (both lay and medical) who have access to the best information, and know how much money is available, decide the disposal of the resources entrusted to them, and so forth.

The appropriate clinical concept, which I am attempting to present and define, is in fact the opposite of this. The senior administrator, whether lay or medical, is in the least favourable position to know the needs of the patient-doctor relationship. He cannot really control; he can only strive to satisfy a demand. The individual patient in his relationship with the doctor originates the demand, and it is the doctor's obligation to formulate this for the benefit and instruction of the administrator. Instead of clinical authority devolving from statute law, and being passed down through a hierarchical system, I suggest that it develops as a need in the individual patient, and has to be passed up through the hierarchy to the statute interpreters and the statute makers; and all the way up the obligation and work of the administrators should be to make possible the best practicable end to the therapeutic transactions between doctor and patient. But even the judgment as to what is the appropriate end to treatment may lie ultimately with the patient, and not with the doctor; and far less with the hospital management committee, regional board, Ministry, or Parliament.

The more complex or urgent a particular administrative decision may be, the more important it is that those responsible for it should go back to the clinician for information. The patient may not always be right in an absolute sense, but he has the privilege of first claim: and only the doctor in the clinical team can know and assess the technical factors involved.

SIGNIFICANCE FOR ADMINISTRATION

With this concept of the clinical situation in mind, I suggest that three kinds of administration can be defined in relation to medical work. They may be termed: (1) clinical administration, (2) supportive administration, and (3) administrative therapy.

CLINICAL ADMINISTRATION

This may be regarded as the administrative duty of every doctor. For the general practitioner, it means organising his surgery, arranging his visits, fixing consultations and admissions to hospital, and so forth. For the hospital doctor, it means ensuring that his patients have what they need for their treatment or welfare—e.g., the proper blankets, the right food, clean walls, appropriate decor, suitable lavatory accommodation, and advantageous drugs. It also means attending to therapeutic relationships, with relatives and hospital staff, as well as with others of the medical and nursing team. There is no difference in principle between the psychiatrist and other consultants in these obligations—any difference is in emphasis only.

One should at this point distinguish between the therapeutic team and the individual clinician, who is usually himself part of a team. It is convenient to look on the clinical team as the therapeutic unit, headed by a consultant, who accepts responsibility for clinical work within the team. At the same time, exactly the same principles apply within the team as in the wider relationships of the team regarded as a unit.

I suggest that, although clinical work can be delegated downwards within a medical and nursing team, with its hierarchical structure, the responsibility for clinical administration always lies with the professional figure in immediate relationship with the patient. The role is

1. Fox, T. F. Croonian lecture. *Lancet*, 1951, ii, 115.

taken up by each successive member of the team in direct contact. Thus the houseman exercises judgment all the time how far he will go both in clinical action and in administrative action, without calling upon his senior, but when the latter takes over he in turn becomes the responsible clinical administrator. When a senior, however, such as a consultant in charge, speaks for all his team towards colleagues or administrators, he is doubling his role. To colleagues and administrators he is the responsible clinical administrator, and his duty is to interpret the clinical needs of his patients, allowing also for the opinions and requirements of his junior staff; but within the team itself his clinical administrative function is intermittent, and he is most of the time acting the part of supportive team administrator to his juniors.

SUPPORTIVE ADMINISTRATION

This is the administrative activity which subserves the clinical situation, makes it possible, provides the resources, and so on. The supportive administrator defers to the needs of the clinician. Outside the medical team he is now usually a layman, except in mental hospitals. He supervises routine administrative work in the hospital, or regional board, but should do so prepared at all times to modify his actions, in so far as this is possible, in accordance with the clinical views transmitted to him. *His responsibility is delegated to him by the clinician; and he must be prepared to surrender it in any given situation, if the clinician requires it.*

It is in this area that much misunderstanding develops, and the responsibility for avoiding misunderstanding lies both with the administrator and with the clinician. Members of management committees and their officials are far too often under the natural impression that their function is to manage the doctors and the hospital concerned, as against the notion of providing a milieu within which doctor-patient transactions proceed, and which should be adjusted to the requirements of the *patient*, transmitted and interpreted by the doctor to the administrator.

Similarly, the notion of " control " of hospital medical staff exerted by the Ministry through regional boards is natural to many who are trained to use mechanical and authoritarian ideas. In fact, however, in our present society, the only " control " which should be exerted on the individual doctor in his clinical work is that imposed by the ordinary Rule of Law in the country, by medical ethics, and by contractual engagements.*

For the clinician the important thing is to distinguish clearly between different clinical needs, and to be able to put them in order of priority, without confusing the supportive administrators. The latter, indeed, although deferring to the clinician, must at times question whether a requirement does in fact derive from patient's needs rather than the clinician's own personal wishes. And one need hardly emphasise that the good lay administrator has experience and training which allows him to contribute expert knowledge to the whole process.

ADMINISTRATIVE THERAPY

By this term one tries to convey the idea of a medical administrator doing good for people, and arranging for their treatment. He is to be distinguished from the doctor who is filling the role of clinical administrator, however, in that he does this at second hand, through assistants whom he directs to carry out certain required clinical duties. Administrative therapy can be distinguished from supportive administration in that the latter derives its significance from the patient-doctor transaction, which is the starting-point for the whole process. In administrative therapy, the medical administrator initiates and indeed often imposes the therapeutic programme, because of his specialised knowledge and his legal powers; and the patient conforms.

There is clearly a place for this medical activity, as can be seen readily in the discharge of statutory obligations in the fields of public health and the Armed Services, where, in fact, sanctions to compel treatment under administrative direction have been invaluable. It is unlikely, however, that there is any place for administrative therapy in a hospital setting, including mental hospitals, unless possibly in dealing with infectious diseases. Even then it becomes unnecessary if an effective medical staff committee is functioning. Administrative action relating directly to a patient, and which is therefore at first hand, comes into the category of clinical administration. Administrative action which derives from clinical work and is delegated by the clinician is supportive. If a hospital administrator in ordinary circumstances claims that his role is that of administrative therapist, rather than supportive administrator, it is most likely that he is indulging authoritarian needs in himself which will actually in the end restrict and hamper clinical administrative work by his colleagues, and especially his juniors.

MEDICAL ADMINISTRATION

The roles of clinical administrator and administrative therapist clearly belong to those who have had medical training. If a doctor takes part in supportive administration outside the clinical team, however, as for example, in a regional board, or at the Ministry of Health, he should do so only because his special knowledge allows him to understand the needs of the clinician without elaborate discussion, so that he becomes interpreter to the laymen. He himself remains a supportive administrator distinguished only by his specialised knowledge.

Medical superintendents have in the past attempted to combine the roles of supportive administrator and administrative therapist, and are still trying to do so in mental hospitals. Success, however, involves tight-rope agility. In practice, inevitably, as a medical superintendent gets older and more experienced his personality imposes greater and greater rigidity on the situation, with corresponding frustration for the hospital staff. The extent of the problem in the mental hospitals has only recently been realised. The " famous " superintendent is likely to be the man who has successfully mixed support and imposition in such a way as to gratify something in himself, with ultimate domination of his colleagues. The " good " superintendent is probably the man who consistently subordinates his administrative therapeutic activity to his supportive function; or even succeeds in eliminating the former entirely, and who thereby encourages the best in his colleagues to come out.

THE THERAPEUTIC COMMUNITY APPROACH IN PSYCHIATRY

In recent years a tendency has developed to describe the successful mental hospital as a therapeutic community.

* If the last of these ever becomes wide enough to allow of administrative control of an individual patient-doctor transaction, as seems possible in the National Health Service at this time, it will invalidate the concept under discussion. There may therefore be good reason to revise the contractual terms under which individual doctors work in hospitals.

There is, however, confusion over what is actually meant by this phrase. No definition seems to have been reached, and often only a vague notion of benevolent intention is conveyed, involving rehabilitation as well as custodial care in the mental hospital. The Therapeutic Community approach to treatment is a different matter, however, and is a well-understood clinical administrative procedure of a special kind. It is described extensively in this country by Maxwell Jones.[2] The following characteristics have been taken from various publications of his:

1. A relatively ordinary and familiar social environment is provided for the patient so far as relationships are concerned. This means minimising any social factor in the process of hospital care or treatment which emphasises differences from social life outside the hospital.

2. The patient is made increasingly aware of the effect of his behaviour on other people, and so obtains some degree of social insight.

3. The whole population of the clinical unit concerned takes part in regular community meetings as a matter of therapeutic technique.

4. Trained staff enter into as many as possible of the diverse and fluctuating group situations, including informal (and unplanned) as well as formal social and therapeutic groups. By this means, together with the unifying influence of the community meetings, psychotherapeutic treatment is applied over the whole twenty-four hours, and is not limited to, say, a formal daily, or perhaps weekly, psychotherapeutic session.

5. The authority structure of the unit is "flattened" in such a way as to allow patients and staff members with lesser responsibilities to share authority. This process involves blurring of staff roles when seen from the uninformed point of view of the patient, but requires sharper understanding of role-playing by the staff.

6. The freest possible channels of communication are created between the individuals, both staff and patients, who make up the community.

A permissive interpretative agnostic regime of this kind is almost the opposite of the administrative therapist's approach. Application of item no. 5 by a consultant in a hospital with an administrative therapist as medical superintendent would be impossible without conflict, because for full success it requires above all good supportive administration.

It is better, therefore, to use the term "administrative therapy," as Clark [3] does, to describe the organisation of a hospital by an administrator to promote second-hand therapeutic benefits for the patient. This can certainly have dramatic results in a hospital which has been stagnant. For the reasons given already, however, they are very liable to be temporary, and will produce a state of conflict if there are conscientious senior clinicians on the staff. It is important, therefore, for anyone working in such an environment to appreciate that he must be prepared to subordinate his own views about treatment to those of the administrative therapist (who is, of course, usually a medical superintendent) and the staff of such a hospital must, for success, identify with and be loyal to their chief.

Sometimes an administrative therapist breaks the bounds of his hospital and proceeds to apply his personality in wider fields. It is reasonable to use the term "community therapy" for this (Macmillan,[4] Carse et al.[5]). Here again, however, we have to question whether it is in fact for the good of the patient to establish this kind of approach. We must always be on our guard against the temptation to know what is best for the populace. For certain selected inadequate groups of people, however, something of this kind may be clinically acceptable.

2. Jones, M. Social Psychiatry. London, 1952.
3. Clark, D. H. *Lancet*, 1958, i, 805.
4. Macmillan, D. *ibid*, 1958, ii, 201.
5. Carse, J., Panton, N. E., Watt A. *ibid*. 1958, i, 39.

RELATIONS BETWEEN CLINICIANS AND ADMINISTRATORS

These are, of course, of prime importance. Many people do not question the significance of different kinds of relationships, except in terms of our social culture. In other words, they react intuitively, or on the basis of education. For the psychiatrist, however, it is appropriate to examine relationships in a more detailed and perhaps self-conscious way.

There are obvious differences in personality between most clinicians, who have been trained intensively towards individuality, and the kind of person who is a good committee administrator, or hospital executive. The former is impatient of circumstances, and of people, who frustrate his attempts at being effective; and the latter is equally impatient of those who apparently cannot see beyond their own needs. On both sides exceptionally strong personality characteristics may have to be allowed for; and what is required in hospital affairs is an arrangement which successfully takes care of the problems created by such "difficult" individuals, on both sides, as well as ordinary hospital routine.

The matter can perhaps be usefully approached in terms of role-obligations and communications. Given good understanding of clinical and administrative obligations respectively, the chances of faulty relationships developing are greatly reduced. For brevity, they can be summarised as follows:

Obligations of the Clinician	*Obligations of the Supportive Hospital Administrator*
To establish good understanding with the patient; and use it as profitably as possible on his behalf.	To ascertain the requirements of the clinician, and provide the resources requested.
To judge the material and psychological needs of the patient.	To advise the clinician on, and take delegated responsibility for, the day-to-day administrative arrangements within the hospital.
To satisfy these needs (i.e., treat).	To advise the clinician on any established administrative circumstances which may affect clinical work (mainly policy, or financial limitations).
To inform the administrators what is required for proper treatment, and of any imbalance or deficiencies in the resources available.	To collaborate with the clinician in modifying such established administrative limitations when clinically appropriate.
To decide the order of priority for administrative action when necessary.	

Formal machinery is required which, when properly used, will encourage both clinicians and administrators to understand and fulfil their separate roles. So far as clinicians are concerned this exists potentially in the medical advisory committee system; although it is made ineffective when a medical superintendent attends hospital management committee meetings, so that it is inevitably short-circuited. Moreover, it is easy for clinicians to forget their roles. Thus, a common tendency for doctors in committee is to identify with their supportive administrators, and instead of reaching a recommendation on straightforward clinical grounds to anticipate administrative reaction and bend to it in advance. While giving participants an illusion of responsibility, this practice is in reality evasive, and probably cannot result in a progressive hospital.

It is in facilitating communication that the supportive administrator can be specially effective, and it is in this that many administrators have shortcomings. There are specific ways in which he can make himself specially effective. It is scarcely possible to communicate too much or too often. The initiative should come from the administrator. It is his responsibility to keep the wheels turning as fast as possible, and it is by speeding communication that he can do this. Personal contact is very desirable. He should, therefore, make regular visits to every senior clinician, to provide opportunities for the latter to refer back to him the problems which he will usually be glad to dispose of: and he should take care to communicate to the clinician the maximum information available on any administrative question at the earliest possible moment. Difficulties arise when the supportive administrator sits in an office expecting the clinician to come to him when the need arises; or indulges the habit of exercising power by retaining information, or by communicating distantly in small terse letters.

Arrangements should obviously be made to bring clinicians and administrators into touch with each other, both formally and informally. Committees are an example of formal occasions for meeting, and when a hospital secretary can act as secretary of a medical advisory committee it can be most profitable. Common-rooms jointly shared by senior administrators and clinicians might be expected to provide good opportunities for informal meetings. No hospital should be without fairly frequent opportunities for management committee members and clinical staff to meet also, but preferably in the clinical setting, rather than in the boardroom or office.

CLINICO-ADMINISTRATIVE CHANGES IN MENTAL HOSPITALS

Most mental hospitals in the meantime retain experienced and active administrative therapists in the form of medical superintendents. When the Mental Health Act is fully operative, however, we can expect the emphasis on clinical administration to increase, and that on administrative therapy to diminish. Taking the shortage of psychiatrists into account this can only mean the ultimate abandonment of the medical superintendent system.

The question we must ask is how much the patient may not lose as well as gain in this process of change. If he loses it is likely to be in the arrangements for supportive administration rather than in clinical work. The question then becomes simply whether a lay supportive administrator will be less effective than a medical supportive administrator. On the face of it there seems no reason why he should. It depends on how well he understands his supportive role, and his ability to be a good administrator.

There is considerable room for experiment, because adaptation of the present system must clearly be gradual. Moreover, although the medical advisory committee system in general hospitals is well established, nobody is likely to claim that it is beyond improvement. And it is an unverified assumption that a specialised unit, such as a psychiatric hospital, should have the same administrative structure as a general hospital. Thus, if general-hospital psychiatry develops and at the same time the present mental hospitals start to accommodate other specialties than psychiatry, it may be that lessons for the general hospital can be derived from the adjustments now open to former mental hospitals.

The kind of experiment which we may hope for might involve, for example, medical advisory committees (or possibly a subcommittee) meeting weekly or twice weekly instead of monthly, and so maintaining a much closer running contact with day-to-day affairs of the hospital. The hospital secretary could attend, both to keep records, and to be able to put the committee's decisions quickly into effect. There might also be routine daily contact between the hospital secretary and the chairman of the medical advisory committee: and the latter might indeed hold office as chairman on a weekly, fortnightly, or monthly rotating basis, so that liaison over supportive administration for the whole hospital would be a periodic rotating duty amongst the senior clinicians. In this way the needs of a specialist hospital might be met more satisfactorily than by using an arrangement devised for a large general hospital, with its widely differing clinical units.

Similar experimental adaptation might be made in communication between the medical staff and the management committee. Administrators generally, both committee and executive, should consciously and deliberately accept that their administrative work derives from and is delegated by the clinician. This means that in discussion they should represent and act for the clinician; and defer to his views whenever any doubt exists. Good communication is therefore essential. By inviting the chairman of the H.M.C. routinely to attend, for example, the M.A.C. meeting immediately before any H.M.C. meeting he would be enabled to hear the views of the M.A.C. on doubtful topics, and also to approach his committee with better information than he would otherwise possess. Such a procedure might substitute for a medical superintendent attending the H.M.C. The appointment of a member of the medical staff to the H.M.C., not as a delegate, but as a full member whose duty would be to encourage reference back to the M.A.C. of doubtful questions, would round off this arrangement, and provide further assurance of good mutual understanding.

These suggestions are put forward to illustrate possible developments and not as specific proposals. What is required is perhaps the maximum flexibility, wide opportunities for discussion and reporting of results, and good information amongst senior staff, both clinical and administrative. The final outcome of all clinico-administrative interaction depends, of course, on personalities. Selection and training are therefore important factors in achieving happier and more successful hospital units. Whereas this implies recognition of lay administrative skills, and perhaps their reward, in a way not hitherto allowed for in the hospital services, it also implies an addition to the overcrowded medical curriculum; but there is perhaps an advantage over competing subjects in that clinico-administrative training may fit in best after rather than before qualification. For example, attendance at meetings of medical advisory committees during the preregistration period might prove for most doctors a relatively painless introduction to these procedures, understanding of which has insidiously become more and more important for the welfare of the patient since 1948.

SUMMARY

It is suggested that administration in medicine has special features resulting from the patient-doctor relationship, and it is conceived as of three types:

(a) Clinical administration—the responsibility of every doctor.

(b) Supportive administration, mostly lay, which makes clinical work possible, and amounts to delegated clinical administration.

(c) Administrative therapy—the expression of a doctor's personality in the control of therapeutic situations at second hand.

There seems little reason for a doctor to play the part of supportive administrator, either in mental or general hospitals: but there may be at regional boards or in the Ministry of Health. There seems no place for administrative therapy in hospital work.

The concept of the therapeutic community as the creation of an administrator is considered to be fallacious, and is contrasted with the therapeutic-community approach to treatment, which is regarded as a skilled clinical administrative technique.

The obligations of the clinician and the administrator are reviewed, and the importance of communication in administration is stressed. Examples of possible adaptation of mental-hospital administration under the new Mental Health Act are described.

Although the views expressed here are my own, I should like to acknowledge the many discussions with colleagues in the Group for Representation of the Views of Clinical Psychiatrists, which have helped me to clarify and formulate them.

Special Articles

THE SERIOUSLY ILL PATIENT AND THE HELICOPTER

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SINCE the Scottish Air Ambulance Service was formed in 1933, it has expanded until the area of operations now covers the whole of Scotland, including the Kintyre Peninsula, the Hebrides, and the Orkney and Shetland Islands.

Although the Isle of Wight is not situated as remotely as these islands, and has ample accommodation for the more common acute medical and surgical emergencies, some acutely ill patients need to be transferred as quickly as possible to special units on the mainland for neurosurgery, plastic surgery, spinal injuries, or respiratory poliomyelitis.

In the summer of 1947, one of us (J. M.) arranged for a child, with hæmorrhage into a cerebellar tumour, to be flown from the Isle of Wight to Croydon airport. In June, 1953, the county council approved a proposal for transferring patients by air to the mainland in exceptional circumstances, but the possibilities of air transport were not investigated again until July, 1955. The Flag-Officer, Lee-on-Solent, was then asked whether a Royal Naval helicopter could be available to transfer patients seriously ill with poliomyelitis from island hospitals to the mainland. He replied that, although the primary task of the helicopters was naval training, in certain circumstances assistance might be given. Trial landings were made at Fairlee Hospital, Newport, and at St. Mary's Hospital, Portsmouth. In June, 1956, we were told that the Admiralty had approached the Ministry of Health, which had agreed that exceptionally, when no other form of transport was practicable, transport by helicopter might be arranged. In the Isle of Wight each request by the consultant in charge of the patient is considered by the county medical officer or his deputy, who gets in touch with the appropriate Service station.

Between July, 1956, and August, 1959, eighteen helicopter flights carried patients from the Isle of Wight to mainland centres.

The diagnoses of the nineteen patients (of whom six were visitors) involved were: subarachnoid hæmorrhage (6); burns (4); fractured skull (2); acute polyneuritis (3); fractured spine (2); spinal tumour (1); and tetanus (1). The destinations were: Atkinson Morley's Hospital, Wimbledon (6); Infectious Diseases Hospital, Portsmouth (4); Odstock Hospital, Salisbury (4); Hospital for Sick Children, Great Ormond Street (2); and Stoke Mandeville Hospital (2). Eleven patients made partial or complete recoveries, and eight died, mostly within a few days of transfer. Three patients involved in the 'Aquila' flying boat disaster were transferred to Odstock Hospital by air, two on Nov. 16, 1957 (one who sustained about 70% body burns died within 24 hours, but the other has recovered despite severe burns of the face and hands in which he lost his nose, both ears, and all the skin of his scalp, face, and neck); another, transferred on Nov. 23, who had a severe head injury as well as burns of the arms and legs, died on Dec. 6 without regaining consciousness.

The cost of flights by Service helicopter varies from £85 to £115 per flying hour; hence the charges for a flight to the London area from the Isle of Wight range from £150 to £198. A similar flight by B.E.A. helicopter (to Battersea) would cost about £100, by B.E.A. 'Dakota' (to London Airport) about £80, and by De Havilland 'Rapide', hired from Portsmouth Aero Club to Fairoaks, near Chobham, about £20.

DISCUSSION

Helicopters were of much value in removing casualties from the jungle during the Malayan and Korean campaigns, and from behind the lines where airfields were impracticable (Edwards 1958). Westland 'Dragonflies', 'Whirlwinds' and 'Widgeons', and Bristol 'Sycamores', have pioneered air-rescue work around the British coast. American Forces have also helped with their Service helicopters in various emergencies—notably the wreck of the Goodwins lightship. For high-altitude work in the Alps, special helicopters have been evolved, such as Sikorsky models and the French turbo 'Alouette', the use of which was illustrated dramatically in the Mont Blanc tragedy in January 1957 (*Lancet* 1958).

Indications for Air Transport

Although, as a general principle, a surgical or medical team should go to the patient rather than the patient to the team, patients with leaking cerebral aneurysms, late-diagnosed subdural hæmorrhage or meningeal hæmorrhage, acute respiratory paralysis from poliomyelitis or polyneuritis, and spinal injuries, may justifiably be transported by air. Patients carried more than 50 miles and at night should travel by fixed-wing aircraft.

In a Memorandum on Accident Services (1959) the British Orthopædic Association recommends that patients involved in accidents should be admitted to accident units, providing between 150 and 250 beds per half-million of the population. Lewin (1959) suggests that patients with head injuries should be transferred, if necessary, by helicopter, to a limited number of neurosurgical centres, and McKissock (1959) "would like to see a regular service between the various hospitals on the South coast and Atkinson Morley's Hospital". Guttmann (1959) thinks that two patients transferred from the Isle of Wight would not have survived transport by road.

Limitations of Air Transport

Patients need to be transported to and from the take-off and landing sites, and their condition may be adversely

affected by transfer on and off stretchers. Flying to a large extent depends on the visibility in the vicinity of aerodromes, and low cloud and fog may lead to delays and cancellations.

Although in January, 1958, it was impossible because of fog to transfer by air an island patient to Atkinson Morley's Hospital, he was taken by road and admitted at least 12 hours before the journey could have been made by air. Aircraft may not be available immediately, as in the case of a request for air transport in August, 1959, when a patient began to bleed severely during bronchoscopy; the surgeon accompanied him during transfer by ambulance and boat to Portsmouth, and the patient arrived at the hospital as soon as if he had awaited the first available aircraft.

Under certain meteorological conditions, turbulence may make fit passengers airsick, and in seriously ill patients, particularly with paralysis of the muscles of swallowing, this may lead to grave complications. The ability of helicopters to "lift" crew and passengers depends on air temperature and wind velocity; on a hot windless day it may be impossible to carry a crew of two with patient and escort, and the navigator must be left behind. Service helicopters are not specially designed for carrying patients, and doctors or nurses may have to lie on the floor; noise and vibration is considerable and there may be some smell of fuel. Seriously ill patients may become increasingly apprehensive, and, if predisposed to travel sickness, they may suffer from nausea, retching, or vomiting.

Technical procedures are more difficult in aircraft, and, because the electrical voltage is 24, a lung inflator used for artificial respiration needs a special motor or batteries. Hand inflation is not a satisfactory alternative except for short periods, because patients are always less comfortabe when inflated by hand and movements of the aircraft make the procedure harder (Sandiford 1957). Increasing height leads to lower oxygen tension, and, despite oronasal oxygen, careful consideration must be given to patients with a hæmoglobin level of 50% or less, with severe chest injuries, with impaired cardiorespiratory functions, and with facial injuries which prevent the use of oxygen masks. Reduced atmospheric pressure renders coughing less effective and reduces the efficiency of certain respirators. Upper-respiratory-tract infection and involvement of the pharyngeal muscles increase greatly the risks of air transport.

Air Transport in England and Wales

Inquiries made to local-health authorities in England and Wales established that two county councils—Cornwall and the Isle of Wight—and three county-borough councils—Exeter, Ipswich, and Plymouth—had mentioned air transport in their schemes under Section 27 of the National Health Service Act (1946). Two county councils and one county borough had used and paid for commercial air transport, and fifteen county medical officers and eleven county-borough medical officers mentioned that Service aircraft had been used to transfer patients in their areas.

CONCLUSIONS

The transport of seriously ill patients by air has a definite and increasing part to play in the local-authority ambulance service in England and Wales. The medical officer of health of the local health authority should act as a referee before application for an aircraft is made to a Service air-station or to a commercial airline. Although air transport will be life saving in some cases, occasional errors may be made.

Helicopters may fulfil a useful role in evacuating patients seriously injured in a major accident, and they may be used increasingly to transfer patients to the kind of accident unit advocated by the British Orthopædic Association. There are risks involved, because the accident-rate for helicopters is higher than that for fixed-wing aircraft.

The cost of air travel is high, especially for areas which are remote from the main hospital centres of the country.

We are glad to acknowledge the assistance in the preparation of this paper of colleagues in general medical, hospital, and public-health practice, and in government departments. The views expressed in the conclusions are our own.

REFERENCES

British Orthopædic Association (1959) Memorandum on Accident Services. See *Lancet* (1959) ii, 178.
Edwards, A. G. (1958) *Lancet*, i, 470.
Guttmann, L. (1959) Personal communication.
Lancet (1958) i, 468.
Lewin, W. (1959) *Brit. med. J.* i, 131.
McKissock, W. (1959) Personal communication.
Sandiford, H. B. C. (1957) *Lancet*, ii, 823.

The Widdicombe File

LXIII—MEDICAL ILLUSTRATION

DEAR DR. G.,

At the Annual Staff Dinner last week your nephew, who I am glad to say was not driving himself home, showed me a letter that he had received from you containing some criticism of the Department of Medical Illustration.* Perhaps you would be so good as to listen to the other side of the picture.

Concerning the young man whose recovery to normal health was illustrated by A.P. and lateral views of his face, I checked the photographic request form. The request, unsigned of course, after much deciphering reads "to show improvement". My assistant tells me that the patient had apparently little recollection of the accident which presumably had involved him in your nephew's heroic treatment. Checking our files, however, revealed that he had been previously photographed by us for Mr. S. of the E.N.T. department (they also omit to sign their forms). It therefore seems reasonable to repeat these views, which had been taken prior to an operation for rhinoplasty.

You are right that Mr. Bronson's seminar on audiovisual aids at Kansas University had enabled him to speak with authority on his project of "The underlying motivation in audiovisual instructional techniques". However, his studies had not enabled him to appreciate that it is not worth making a lantern slide containing three minutes of reading matter when (*a*) he will be talking all the time, (*b*) as he says, the slide is only on the screen for thirty seconds, and (*c*) the lettering on the slide is only legible to the first row of the audience.

You might use your influence with Mr. Bronson to ask him to limit his requests to illustrations that he really needs. We should then have time to prepare one set suitable for slides and another for publication.

Incidentally, rummaging on a shelf in the registrar's room I came across 73 clinical pictures taken for you during the past two years. You might be interested to see these some time. When you come round there are also those urgent prints for publication that we did at twenty-four hours' notice Tuesday week ago.

Yours faithfully,

S. WIGGLESWORTH.

* This letter was reproduced in our issue of July 16, p. 147.—ED. L.

In England Now

A Running Commentary by Peripatetic Correspondents

I HAVE never discovered why my brother sent me a brandy-snifter from Winnipeg. It stands about 15 in. high, and would hold, if I cared to fill it, about a gallon of brandy. Unfortunately I do not care for brandy except in rather smaller quantities, and until recently I had found no use for the unwieldy receptacle. It was not until I was buying some weed for the goldfish tank in our ward that I decided to turn my brandy-snifter into an aquarium.

I bought some more weed, and a bag of gravel, and planted the former in the latter at the bottom of the glass which I had half-filled with water. Next day I went to the public library and borrowed a book on aquaria. It was rather discouraging. I learnt that I would only be able to keep the very smallest fish, and that I should not venture to acquire even these until the weed had become properly established. Gloomily I studied the various kinds of weed illustrated, and decided that the type I had must be a South East London variant, as it did not seem to be known to the writer of the handbook. The outlook for my career as an aquarist did not seem bright, and I went on holiday expecting to find disaster on my return.

Five weeks later, the weed is growing vigorously, and the glass is full of bright green shoots from which arise streams of bubbles of what I presume to be oxygen. The water has remained clear and odourless; but the greatest marvel is that in the previously sterile tap-water has arisen a colony of small water snails. There is also at least one water beetle, several worm-type creatures, and something which resembles a transparent dragon. Since spontaneous generation has, I believe, been disproved, I assume that all these beasts, or their eggs, were lurking in the weed. Clearly I cannot introduce any fish until the snails are big enough to be indigestible, but I have put in a few water fleas as a possible alternative diet for the future occupants.

The only snag to this new hobby is that I can never again give a party, lest any inebriated guest should drink the fish.

* * *

Poliomyelitis vaccination is no longer news, but even routine work is not without its human interest. Raising the age-limit to include the " under-40's " had interesting results, for example. Birth certificates are not demanded, otherwise some of the very mature " 39s " who have passed under my syringe might have been embarrassed. Does a woman of 45 request vaccination as an " under-40 " because she is scared of poliomyelitis and not too scrupulous about the rules? Or does she volunteer, to convince her inquisitive and unconvinced contemporaries?

We have polio sessions (no, I don't care for it either, but take your choice, conformity or pedantry) in all the usual places: village halls, schools, clinics, back rooms, front rooms, even bathrooms and kitchens. The best one, I think, is the evening one in the youth club where I hope to increase the " over-15 " response by taking " herd valour " on our side. Bert Higgins wisely didn't volunteer for anything—his dad warned him about that—but he finds it difficult to stand out of line when his mates and their girl friends are lining up nervously, left hand on hip, and offering to catch each other as they faint.

With the smallest encouragement this could be turned into a vaccination conga, because the record-player blares on without interruption. I like working to the accompaniment of the Top Twenty; after all there is a rhythm in making a series of injections, just as there is a beat to *Cathie's Clown* and *Running Bear*. It's not always the right beat, of course, but you can't have everything. Some of the titles are singularly appropriate too. *Do you mind?* and *Hit and Miss* both strike the right lighthearted note but *Mack the Knife* is a shade on the macabre side. Fortunately he is out of favour now. I wish they would turn the volume down just a little though. It worries me when I remember that the last club leader was deaf. Either that is why the records are played so loud or . . . could it be *because*? But he was there every evening, I only go once a month.

* * *

When we returned for the second year to the Scottish island on which we are carrying out an archæological survey, we were greeted as old friends by the hospitable islanders, and invited to a ceilidh which they had arranged for us in the dining-room of the hotel in which we were staying.

The party got off to a fine start when a kilted piper came in and marched up and down to suitable music. Whisky began to flow. Sets were made up for various dances, and no-one was allowed to plead ignorance. Each dance continued until even the slowest-footed Sassenach had the hang of it, and was not only swinging his partner about boldly but uttering appropriate yells as he did so. One after another of our hosts stood up to sing in English or Gaelic, while we remained shamefully mute. Suddenly the whisky took effect, and the quartet which had been practising the national anthem of the ancient Britons rendered it with great enthusiasm. From then on it was a question of who could get to the piano first; and to show that the Scots didn't have a monopoly of foreign languages, two of our party sang a song in Welsh.

A few days later we went to another ceilidh. This time we danced on the beach by the light of a bonfire to the music of the pipes. Before our next visit to the island we intend to learn a few more songs. We can't manage a piper, but if we start now some of us might achieve a tune or two on the recorder.

* * *

Psychotyping is, by now, a well-established technique and is based on three tests: of distance run towards a standard meal in face of a constant restraint; sleep threshold during a dull lecture; and the quantitative profiles of the area-time products for blushing on exposure to a series of standardised social embarrassments. Using these tests, three groups have been distinguished; ectopsyches, mesopsyches, and endopsyches. The last group have food as a dominant incentive under all conditions while the first group are concerned exclusively with collecting and processing information which need be neither useful nor relevant. The mesopsyches are unable to keep still.

A positive correlation between endopsyche and fatness was established, and weaker, still positive, correlations were found between muscularity and mesopsyches and between height/weight ratio and ectopsyche. That mental attributes can determine body form is an exciting new prospect opened by these investigations.

* * *

Do you believe in fairies? I presume Shakespeare did, but it may have been a midsummer's night dream. These thoughts occurred to me when, early in June, I was sitting in my garden in his native county of Warwickshire when I found that a snake had left his, or her, enamelled skin in some pampas grass which grows in the middle of a small goldfish pond. The skin was absolutely complete and I had only to move a pampas shoot to get it out whole. It was $2^1/_2$ ft. in length and 2 in. in diameter in its widest part and it only tapered at the tail. I suppose this was the sort of snake which was common in Warwickshire in Shakespeare's time; we usually see two or three every year in our garden. If this enamelled skin is " Weed wide enough to wrap a fairy in " they are much smaller than I supposed.

* * *

*Ode to the I.C.B.M.s**

Atoms come and atoms go
(Though mine form mainly H_2O)
Polypeptides pass away
(Not forgetting D.N.A.)
Up or down the double spiral
(This way heaven and that hell-fire-all)
Cloud on cloud goes floating free
(Can perhaps this one be me)
You, too, could be a gamma ray
(All change! from Mass to Energy).

* Intercontinental Ballistic Missiles.

Letters to the Editor

VALUE OF A LARGE DOSE OF ANTITOXIN IN CLINICAL TETANUS

SIR,—Professor Brown and his colleagues (July 30) in Ibadan, Jamaica, and London have performed a most useful service by demonstrating the therapeutic value of a large dose of A.T.S. given after the onset of the symptoms of tetanus. We hope that we shall not seem ungrateful if we say that their paper has made the position more difficult for general practitioners in this country. The great majority of people in Great Britain who sustain a cut which merits being stitched are given prophylactic A.T.S. This is good treatment for that particular cut, but lays up trouble for the patient in the future. He is likely to be immunised to horse serum by the prophylactic injection of A.T.S., so that not only is any future prophylactic or therapeutic injection likely to be ineffective [1] but also the patient is exposed to the danger of anaphylactic shock. This situation has been exemplified by a recent patient of ours, a 17-year-old boy.

In 1955 he was treated in a casualty department for a cut and received prophylactic A.T.S. In 1960 he was treated in another casualty department for a fairly severe cut received playing rugby football, and again received prophylactic A.T.S., but this did not prevent him from developing tetanus nine days later. His tetanic spasms became severe, and could not be controlled by measures short of paralysis by curare. As part of his treatment, it was decided to give the patient A.T.S. Test doses as recommended by the manufacturers of A.T.S. were given, but none of the stated contraindications developed. Promethazine ('Phenergan') was given by intramuscular injection and the dose of A.T.S. was begun intravenously. After only one-tenth of the therapeutic dose had been given, intense anaphylactic shock developed which as nearly as possible killed the patient. In spite of the severity of the tetanus and the absence of therapeutic A.T.S., the patient ultimately made a good recovery.

In Africa and Jamaica patients with relatively minor injuries are probably not given prophylactic A.T.S. as often as in this country, so that the problem of anaphylaxis hardly arises. The case described above underlines the potential dangers of A.T.S., in this country and also the responsibility of any doctor who gives A.T.S. to ensure that his patient is at least offered active immunisation by tetanus toxoid at a later date. We know a general practitioner who gives tetanus toxoid to patients to whom he formerly gave prophylactic A.T.S. following this injection with a second if the patient can be induced to attend again. We would welcome an authoritative review of the position of A.T.S. in this country in respect of prophylactic and therapeutic injections.

Artificial Respiration Units,
United Oxford Hospitals.

J. M. K. SPALDING
A. CRAMPTON SMITH.

STERILISATION OF THE DIABETIC'S SYRINGE

SIR,—How often should a diabetic sterilise his syringe? In the limited library at my disposal, this subject is glossed over or entirely ignored in most textbooks, and I have found definite advice in only one [2] where sterilisation was recommended once a week.

The pamphlets enclosed with vials of insulin (Boots) recommend that syringes and needles should be "periodically" cleaned by boiling; and these instructions, read by thousands of diabetics, seem exasperatingly vague. It is always recommended that the syringe be kept in surgical spirit.

The verbal instructions given by nurses seem much more clear-cut, and as most diabetics receive their first instruction from the ward sister, those instructions will probably carry most weight. I recently asked 16 nursing sisters in this hospital what they had been taught to teach the diabetics under their care (eight had been trained in London hospitals, four in other parts of England, two in Glasgow, and one each in Holland and Australia). With 1 exception, I was told that the syringe should be boiled daily, immediately before use, and afterwards should be rinsed in water and (usually) left in surgical spirit until the next day. The techniques varied only in minor details.

It seems likely, therefore, that most diabetics are advised to sterilise their syringes daily, a procedure that must take a minimum of fifteen, and probably twenty minutes or more.

I hold very different and perhaps, heretical, views on the need for daily sterilisation; in fact, I confess that I have not been boiling my syringe, needle, and container on more than four occasions annually for over seventeen years. In 1942, the late Dr. J. Wilkie Scott, of Nottingham, gave me some excellent advice in reply to my query as to what type of syringe and container I should buy for my own use. "Buy the best . . . one that will last a lifetime." At that time there were only glass syringes with metal plungers on the market, but the quality varied considerably, and I bought the best available. There were two types of container on offer, which are still commonly used today: the rectangular metal box with detachable lid containing a loose tray fitted with clasps to hold the various parts of the dismantled syringe and needles; and the cylindrical container fitted with a screw-cap, which will hold an assembled syringe (with its needle attached) firmly by the metal shoulder of the syringe, the needle touching neither the bottom nor the wall of the cylinder. The latter container has the advantage of being leak-proof and the disadvantage of being considerably more expensive. I bought the latter.

After a short period of experimentation I developed the following technique for sterilisation:

> The dismantled container, syringe, and needle are wrapped in a clean handkerchief and boiled in a saucepan according to usual practice. The water is then decanted and, when cool enough, the syringe is assembled with an aseptic technique and placed in the empty and dry container, which is then screwed together and put aside for the time it is next required for an injection. The technique of handling the syringe each day is extremely simple. The hands are washed and dried as for social cleanliness, and the insulin is drawn up after swabbing the rubber cap and skin with cotton-wool soaked in surgical spirit. There is only one point that needs careful attention . . . a strict "no-touch technique" for the needle, which includes seeing that the needle does not touch the wall of the container as it is being replaced after use. If the needle should happen to touch fingers, &c., it should be resterilised. Surgical spirit is never put in the container, and the syringe is never rinsed with water until the time has come for resterilisation, and this event occurs only when the needle has become too blunt for comfort and requires replacement. One needle usually lasts me about three months, the longest time being just under five and a half months.

It is unnecessary to rinse the syringe in water after use. Every type of insulin contains a small quantity of preservative against bacterial contamination and none of the various types of insulin I have used has ever caused a blocked syringe. I have never had any trace of inflammatory reaction at the site of injection, and I consider it is a safe technique for any diabetic who is sufficiently intelligent to give his own injections.

If the syringe had to be dismantled before stowing away, I would consider the risk of infection too great to advocate this method, and I would never advise a diabetic to get the metal-box type of container, where the syringe must be dismantled daily.

For all diabetics and particularly those who must travel, this method holds many advantages over the orthodox daily sterilisation. The extra money spent in buying a screw-capped cylindrical container is soon recovered in the saving on gas or

1. Littlewood, A. H. M., Mant, A. K., Payling Wright, G. *Lancet*, 1954, ii, 444.
2. Dunlop, D. M., Davidson, L. S. P., McNee, J. N. Textbook of Medical Treatment; p. 354. Edinburgh, 1949.

electricity bills. The greatest advantage, however, is one which only a diabetic can fully appreciate—that extra twenty minutes in bed in the morning.

Queen Elizabeth Hospital,
Khormaksar,
Aden. F. STEPHEN CARTER.

TRANSFUSED BLOOD AND CARDIAC ARREST

SIR,—Your leading article of July 30 on this important subject rightly stresses the use of calcium salts and the danger of cold blood. Le Veen is quoted as having observed that some stored blood contained 23 mEq. of potassium per litre which misleads one to think that 1 litre of such blood would contain 23 mEq. of potassium.

In fact this is the concentration in the plasma of the blood, one bottle of which, allowing for dilution with A.C.D., would contain about 5 mEq. of potassium. This, as you say, is about five times the normal level.

To encourage an anæsthetist to assess the venous pressure of a patient, draped and supine and with a head-down tilt, is to encourage him to waste his time and to divert his attention when he can ill afford to do so. Melrose and Wilson [3] specifically warn against the dangers of potassium when blood is given into an artery, and describe a simple method of reducing the potassium level, yet you suggest giving such blood into an artery rather than a vein.

Your leading articles carry much weight and cannot attempt a comprehensive review of the literature, but when they advocate a procedure which authoritative workers say will increase the very risk it is designed to reduce, I respectfully submit that one or other must be wrong.

Southampton General Hospital,
Shirley, Southampton. P. J. HORSEY.

*** Le Veen wrote: "The right auricular venous pressure is the most important single determination which can be made during surgery. Careful scrutiny of the electrocardiogram yields far less information than a mere glance at the venous pressure . . ." It seems that there may be different views on this matter. Melrose and Wilson discussed the danger of reflux into the coronary arteries of potassium-rich blood when cardiac output is low; their own figures suggest that the danger is small if the blood is less than eight days old. Removing plasma from blood and replacing it by dextran or isotonic saline may be theoretically easy, but not very practicable if everybody is in a hurry and the blood has already been mixed thoroughly on its way to the theatre. The full implications of ionic imbalance after transfusion are only slowly being appreciated, and certainly it is not yet possible to decide what precautions are most useful, though it seems that one of the chief is provision of blood less than seven days old for all operations in which torrential blood-loss may occur. This, of course, raises all sorts of problems of supply.—ED. L.

SIR,—Your important leading article on the danger of cardiac arrest during massive blood-transfusion brings attention to a similar risk in exchange transfusion in the newborn, where a comparatively large amount of blood is used (on an average 80 ml. per lb. body-weight). It has been our practice [4] in exchange transfusion to avoid citrate intoxication by titrating off about 100 ml. of the supernatant plasma-citrate from each bottle, which is slightly warmed to remove ice-cold.

More recently [5] in cases of exchange transfusion I have recommended continuous monitoring of the heart by cardiophone, which when made just audible is in no way disturbing and is reassuring to listen to. Any alteration in heart action is thereby immediately known and appropriate measures at once taken; and it is found that such changes are heard on the cardiophone before there are visible signs of the heart being affected. Where abnormal heart action persists the transfusion is stopped and recommenced, if necessary, when the heart recovers, which it usually does in 6–12 hours.

Such measures may be of use in the cases of massive blood-transfusions which you describe.

London, W.1. D. J. MACRAE.

HEALING OF WOUNDS

SIR,—Your leading article of July 30 accurately summarises a part of our work, but we should welcome an opportunity to describe our experiments briefly in case any of your readers are misled by the reference made to us by Professor Kahlson and his collaborators on p. 230 of your same issue.

We studied the healing of linear surgical wounds by clinical assessment, by histological examination, and by assay of histamine content in five groups of rats [6]:

Group A.—Rats weighing 200–300 g. were given daily intraperitoneal injections of a histamine-liberator substance (compound 48/80) beginning ten days before operation and continued daily until death. The first dose of compound 48/80 was 100 μg., and this was increased daily by 100 μg. up to a maximum of 500 μg. depending on the animal's tolerance.

Group B.—As for group A, the injections being stopped on the day of operation.

Group C.—Normal (untreated) animals.

Group D.—Rats given daily intraperitoneal injections of 0·01 mg. per 100 g. of histamine acid phosphate for 10 days preoperatively, the injections being stopped on the day of operation.

Group E.—As for group D, the injections being continued postoperatively until the day of death.

The tensile strengths of the wounds were determined in a number of animals from groups A, C, and E.

The results showed that (1) group-A wounds, in animals with reduced tissue histamine, were poorly healed at 5 days compared with normal (untreated) wounds (group C); (2) group-E wounds at 5 days, in animals in which injections of histamine were kept up, were healed more firmly than those of group C; (3) groups B and D occupied intermediate positions; (4) the differences between all groups were less apparent by 10 days; and (5) no difference could be demonstrated by 15 and 20 days after wounding. It is apparent that our article is concerned as much with the non-healing of wounds as with their accelerated rate of healing.

Certain of the experiments carried out by Professor Kahlson and his collaborators were concerned with the administration of an oily suspension of histamine dipicrate ("long-acting histamine") daily in doses of 1·5 mg. or 3·0 mg. for five days after the test wounds were inflicted. They found that "exposure in this manner to extracellular histamine did not influence the rate of repair. This finding is somewhat at variance with the histological evidence of the advanced rate of wound healing in rats given intraperitoneal injections of histamine acid phosphate (Boyd and Smith 1959)". Presumably this remark refers to our group-E experiments summarised above.

In our opinion the two sets of experiments cannot be compared because we gave histamine preoperatively as well as postoperatively, while Kahlson et al. restricted the histamine to the postoperative period.

The University Department of Pathology, Western Infirmary, Glasgow. JAMES F. BOYD.
The University Department of Clinical Surgery, Edinburgh. ADAM N. SMITH.

3. Melrose, D. G., Wilson, A. O. *Lancet*, 1953, i, 1266.
4. MacRae, D. J., Riley, F. *J. Obstet. Gynæc. Brit. Emp.*, 1951, **58**, 826.
5. MacRae, D. J. *Lancet*, 1959, ii, 266.
6. Boyd, J. F., Smith, A. N. *J. Path. Bact.* 1959, **78**, 379.

ACUTE PORPHYRIA

SIR,—We are very anxious to hear from any physician or surgeon who has in his care a case of acute porphyria, either in an acute attack or in remission. We have been carrying out studies in this department on the metabolic abnormalities in these patients, and are now in need of more cases to study. We are particularly interested in patients who are in, or who have recently had, an acute attack, but we would gladly visit any doctor who has a case of porphyria under his care and explain in detail the nature of the proposed tests.

Department of Chemical Pathology,
St. Mary's Hospital Medical School,
St. Mary's Hospital, London, W.2.

A. NEUBERGER
F. F. RICHARDS.

TRISOMIC CONDITION OF A LARGE CHROMOSOME

SIR,—We have read with interest the paper by Dr. De Carli and his colleagues (July 16) in which they report the finding of an additional chromosome in a woman said to be a " para-mongol ". It is apparent that the chromosome is not that associated with mongolism, and in interpreting their findings the authors claim to have found a trisomic condition involving a large autosome, but one only showing minimal developmental defects. The authors considered but discarded the possibility that the additional chromosome was an X chromosome. A leading article in *The Lancet* (July 23) suggested that the authors' interpretation should be viewed with caution. We wish to endorse this view, and we believe there to be grounds for the belief that the additional chromosome is in fact an X chromosome.

The patient appears to be essentially a high-grade mental defective, and to our minds the outstanding abnormality she exhibits is the presence of two sex-chromatin bodies in some of her buccal mucosal cells. The only recognised sign of mongolism was some upward obliquity of the outer palpebral fissures. In respect of this, Penrose [1] points out that " the individual signs of mongolism are not specific to the condition but may occur, though less frequently, in other types of cases and even in normal subjects . . . ". The only other finding was some hypoplasia of the genitalia and the breasts.

We should like to raise, in regard to this case, three points which are of general importance in the diagnosis of abnormalities involving the X chromosome. Firstly, in all cases where two sex-chromatin bodies have been found in the nuclei of buccal mucosal cells, an extra chromosome interpreted as an X chromosome has been found. Conversely, no case to our knowledge has been published in which an extra chromosome has been interpreted as an autosome and in which the nuclear sex has been modified from the normal finding of a single chromatin body in females and none in males. One case has been published of a chromatin-positive male mongol by Ford et al.[2]; this patient, however, was known to have the clinical features of both mongolism and Klinefelter's syndrome, and the double pathology was substantiated by chromosome analysis.

The second point is that, as regards size, the extra chromosome found by De Carli and his colleagues falls within the range of chromosomes in which all authorities agree the X chromosome is found (6–12 Denver classification). The authors contend that measurement of the chromosome reveals the additional one to be at the smaller end of this range, whereas most authorities feel that the X chromosome conforms more closely to the larger chromosomes in the range—i.e., nos. 6, 7, and possibly 8. There is no doubt that the X chromosome is difficult to identify, and in this circumstance we feel it unwise to disregard the positive evidence from sex-chromatin studies and the helpful negative evidence from the clinical examination. To rely simply on measurements in the present state of knowledge seems unjustifiable. It could, moreover, lead to an erroneous conclusion if the additional chromosome is an X chromosome that has suffered a partial deletion. Jacobs et al.[3] have shown that such deletions occur. In fact if a small deletion is postulated as the explanation for the discrepancy in length (as suggested in your leader of July 23), such a hypothesis may also explain the rather low percentage of cells showing two sex-chromatin bodies.

The final point to make is that the clinical state of the patient is more consistent with a sex-chromosome abnormality than one involving an autosome. The presence of an additional autosome has always, with one exception, been associated with widespread developmental defects. The single exception is the apparently normal father of a mongol as reported by Fraccaro, Kaijser, and Lindsten,[4] who had an additional small autosome. It is a reasonable supposition that trisomy involving an autosome as large as that in the case of De Carli and his colleagues would produce widespread and severe defects, and it might even be incompatible with life. In contrast the clinical state of this patient is compatible with that associated with a chromosomal sex of XXX. Individuals with this abnormality, on present knowledge, range from those with external genital and breast hypoplasia, accompanied by secondary amenorrhœa, to females of normal physical development and with normal reproductive cycles.[3 5 6]

We believe, therefore, that the most reasonable interpretation of the findings of De Carli and his colleagues is that the additional chromosome is an X chromosome, and that the patient has a sex-chromosome complement of XXX. Also, it is possible that one of the X chromosomes has suffered a small deletion. On the basis of this interpretation the findings on chromosome analysis, sex-chromatin analysis, and clinical examination are mutually compatible.

M.R.C. Group for Research on the General Effects of Radiation, Department of Radiotherapy, Western General Hospital, Edinburgh.

P. A. JACOBS
D. G. HARNDEN
W. M. COURT BROWN
A. G. BAIKIE.

THE SEX CHROMATIN: SINGLE OR DOUBLE?

SIR,—A " double sex chromatin " in a larger or smaller portion of cell nuclei in buccal smears has lately been reported in the triplo-X-female,[5 7 8] a mongoloid patient with an extra autosome,[9] and two patients with an XXXY sex-chromosome constitution.[10] A direct relation between these extra chromosome(s) and the more or less frequent extra heterochromatic body at the nuclear membrane is, however, far from proven. The sex chromatin in the male, discussed by Dr. Poli (July 2), need not necessarily be a direct manifestation of X and/or Y chromosome. There are, indeed, strong arguments against this hypothesis.[11–13] The whole pattern of heterochromatic masses in the interphase nucleus is made up by more than the sex-chromosomes alone. A sufficient remedy against simplification is a glance at a rodent-cell nucleus.

The findings in genetically abnormal (probably for more than an extra chromosome) individuals do not warrant a conclusion about the relations in normal cell nuclei, especially when they

1. Penrose, L. S. The Biology of Mental Defect. London, 1954.
2. Ford, C. E., Jones, K. W., Miller, O. J., Mittwoch, U., Penrose, L. S., Ridler, M., Shapiro, A. *Lancet*, 1959, i, 709.
3. Jacobs, P. A., Harnden, D. G., Court Brown, W. M., Goldstein, J., Close, H. G., MacGregor, T. N., Maclean, N., Strong, J. A. *ibid.* 1960, i, 1213.
4. Fraccaro, M., Kaijser, K., Lindsten, J. *ibid.* p. 724.
5. Jacobs, P. A., Baikie, A. G., Court Brown, W. M., MacGregor, T. N., Maclean, N., Harnden, D. G. *ibid.* 1959, ii, 423.
6. Stewart, J. S. S., Sanderson, A. *ibid.* July 2, 1960, p. 21.
7. Stewart, J. S. S., Sanderson, A. *ibid.*
8. Harnden, D. G., Court Brown, W. M., Goldstein, J., Close, H. G., Macgregor, T. N., Maclean, N., Strong, J. A. *ibid.* 1960, i, 1213.
9. De Carli, L., Nuzzo, F., Chiarelli, B., Poli, E. *ibid.* July 16, 1960, p. 130.
10. Ferguson-Smith, M. A., Johnston, A. W., Handmaker, A. D. *ibid.* July 23, 1960, p. 184.
11. Tjio, H. T., Levan, A. *Ann. Est. Exp. Aula Dei.* 1956, **4**, 173.
12. Ohno, S., Kaplan, W. D., Kinosita, R. *Exp. cell Res.* 1959, **18**, 415.
13. James, J. *Z. Zellforsch.* 1960, **51**, 597.

are in conflict with well-established facts. In rat-liver nuclei only one X chromosome is heteropyknotic in the female,[12] as cited by Ferguson-Smith et al.[10] and in your editorial of July 23; but this is a poor argument for the hypothesis that in the normal human female Barr's sex chromatin should be composed of only one X chromosome. In mammary and granulosa cells of the mouse both X chromosomes are undoubtedly heteropyknotic and show somatic pairing[14]; moreover, the degree of allocycly in rodents is variable and the Barr phenomenon often not demonstrable. There is direct evidence that the Barr corpuscle in the female of higher mammals and man is composed of two separate chromosomes.[13 15 16] This is not a technical artefact, for even in unfixed cells in tissue cultures a division of the Barr corpuscle in two distinct elements can be seen.

Histological Laboratory,
University of Amsterdam. J. JAMES.

CHROMOSOME ANOMALIES IN "BLEB DISEASES"

SIR,—Bagg and Little[17] demonstrated that the progeny of mice whose ovaries had been irradiated with X rays were liable to multiple deformities, especially of the extremities. These deformities were produced by blebs of cerebrospinal fluid escaping from the fourth ventricle through an abnormally patent area membranacea, exerting pressure in the limb buds and other points of contact, and leading to inflammatory reactions at these sites in the embryo. The malformations proved to be inheritable through an indefinite number of generations.

In a previous article[18] I classified ten syndromes of malformation as a separate group, under the name of "bleb diseases". They were: (1) dysostosis multiplex (Pfaundler-Hurler); (2) oxycephaly (Virchow); (3) acrocephalo-syndactyly (Apert); (4) dysostosis craniofacialis (Crouzon); (5) Laurence-Moon-Biedl syndrome; (6) Morquio's disease; (7) pleonosteosis familiaris (Leri); (8) mongoloid idiocy; (9) cranio-carpo-tarsal dystrophy; and (10) Turner's syndrome. Three other syndromes were later added[19] to these ten—namely Sprengel's deformity (undescended scapula), the Klippel-Feil syndrome, and symbrachydactylia.

The reason for separating these syndromes, under the name of bleb diseases, is that they are considered to have a developmental mechanism similar to that of the deformities described in mice by Bagg and Little.[17] I do not consider the above-mentioned 13 syndromes to be necessarily the only ones belonging to this group. As a matter of fact, Sir Arthur Keith,[20] independently of me, added some further malformations to it.

It is of great interest now to learn that chromosome abnormalities are associated with two of these thirteen syndromes. The normal number of chromosomes in man is 46, including the sex chromosomes, XX in the female and XY in the male. In Turner's syndrome, cells are found to have only 45 chromosomes, the Y chromosome being absent. In mongolism, there is an extra small autosome, making a total of 47.

In another condition called polydysspondylism, which shows multiple bony abnormalities of the skull and spine with low intelligence and which has so far not been classified as bleb disease, again only 45 chromosomes were found.

If the analogy postulated between the malformations of Bagg and Little's mice and the bleb diseases is correct, then the chromosome defects now known to be present in some members of the bleb-disease group may throw some light on the cause of deformities of Bagg and Little's mice.

It is known that chromosomes are electively radiosensitive. Since Bagg and Little's deformities were produced by radiation of the ovaries, it is almost certain that they were due to some chromosome damage. It would, therefore, be of great interest to investigate whether some chromosome anomalies could be detected in the progeny of Bagg and Little's mice. Should this be confirmed, the further question arises whether the chromosome damage is directly responsible for the anomalies found at the base of the fourth ventricle, and the consequent leakage of cerebrospinal fluid.

It would also be of interest to examine the chromosomes in the other ten syndromes of bleb diseases. If chromosome anomalies were found in them, this would give an added support for the separation of these syndromes into a special group. In the light of such future investigations it might be necessary to omit some syndromes now included in this group (e.g., Moon-Biedl syndrome), or to include others not yet classified.

It is naturally possible that chromosome damage of the germ cells may occur without injury to the central nervous system. Whether the bleb mechanism is possible without chromosomal damage, only future studies will show. Should the assumed connection between chromosomal damage and bleb mechanism prove to be correct, it will open new vistas for the study of malformations.

Hong Kong. D. ENGEL.

EXTRADURAL HÆMATOMA

SIR,—I read with great interest the article (July 23) by Mr. McKissock. Do the clinical signs of extradural hæmatoma give any indication of the exact position of the hæmatoma? Are hæmatomas in the frontal region more insidious in onset than those in the temporal fossa? I ask this because I saw a boy suddenly die of a frontal extradural hæmatoma 10 hours after falling out of bed. Even in retrospect the only abnormal clinical sign was slight drowsiness. Incidentally this child had no fracture of the skull on X-ray or at postmortem.

West Suffolk General Hospital,
Bury St. Edmunds. ADRIAN M. BAIN.

SHORTAGE OF RADIOGRAPHERS

SIR,—I should very much like to support Dr. Osborne's remarks of July 9 concerning the shortage of radiographers. At his suggestion, lectures have been given in the Edmonton district in the past few months at girls' schools, but it is too soon, yet, to assess the results of these lectures in terms of student recruits, since the age at which students can start their training is 18 years, and the age-groups so far concerned are up to 16 years.

Considerable interest has been shown. In our case, the lecturer was the male superintendent-radiographer, but in every case he was accompanied by the "young, warm, and vital" in the shape of one of the young and attractive female radiographers. She talked informally to the interested girls after the lectures.

In the North East Metropolitan area, a scheme has just been started where five of the board's hospitals carry out the practical training of radiographers, the formal lectures being given, by kind permission, at The London Hospital. By this method, girls in the neighbourhood of the five principal hospitals can receive their training without too much travelling, as the lectures are completed on two days of the week.

Lectures to the schools are followed in a few weeks' time by advertisements in local papers about the joint training scheme, and so far this has produced three students who will begin their courses in September, 1961, in the Edmonton district. There are many other acceptances in the four districts. One of the great difficulties is the wait of one year from passing the necessary G.C.E. O-level subjects, and being old enough to start the training.

I am strongly of the opinion that the shortage of radiographers could be easily overcome by these methods of lecturing and local advertisement, together with a reduction in the age of entry from 18 to 17 years, with qualification at 19 instead of 20.

I suggest that some of the teaching hospitals might issue their own diplomas in radiography, as some of these

14. Ohno, S., Kaplan, W. D., Kinosita, R. *Exp. cell Res.* 1959, **16**, 462.
15. Klinger, H. P. *Acta anat.* 1957, **30**, 371.
16. Klinger, H. P. *Exp. cell Res.* 1958, **14**, 207.
17. Bagg, H. J., Little, C. C. *Amer. J. Anat.* 1924, **33**, 119.
18. Engel, D. *Amer. J. Dis. Child.* 1940, **60**, 562.
19. Engel, D. *J. Bone Jt Surg.* 1943, **25**, 613.
20. Keith, A. *Brit. J. Surg.* 1940, **28**, 173.

used to do, with this younger time of qualifying in mind. Three or four years of such a scheme would end the shortage of radiographers.

I would like to record my indebtedness to Dr. Osborne for suggesting the lectures to schools, to Mr. M. Cruickshank, the superintendent-radiographer who gave the lectures, and the "young, warm, and vital" ladies who accompanied him.

North Middlesex Hospital,
London, N.18. T. E. BROADBENT.

CUFF HYPERTENSION

SIR,—I was very interested in the letter from Dr. Orma and his colleagues (July 2) and promptly measured the rubber bags used in the sphygmomanometers in this department. All were 21·25 cm. long by 12 cm. wide. These cuffs have been in use for the past six years and I have not noticed any alarming incidence of hypertension.

Since reading Dr. Orma's letter I have paid particular attention to the readings obtained (*a*) where the bag completely encircled the patient's arm, and (*b*) where the circumference of the arm was greater than the length of the bag. In the latter group I have been taking two readings, one with the bag overlying the brachial artery and the other with the bag applied over the outer side of the arm leaving a gap over the artery.

Although I have not had any hypertensive patients in group (*a*) during the past three weeks the two readings obtained in group (*b*) have never varied by more than 5 mm., and most of the readings have been within the normal range.

I am wondering whether the lack of "hypertensives" we encounter could be due to the length of the cuff (90 cm.) which enables it to be wrapped several times round the normal arm.

Medical Department,
Southern Gas Board,
Southampton. MICHAEL B. CARSON,
Chief Medical Officer.

HUMAN BLOOD-GROUPS

SIR,—The appearance of Dr. Fulton Roberts' brochure, *An Introduction to the Human Blood Groups*, which you commend in your review of July 16, indicates that the quality of blood-group research in England has reached its lowest point. Instead of being a scientific treatise, this pamphlet is written like a religious tract, taking its theme from the Race-Sanger book, which has become the British blood-group Bible, and which is the best-known source of *mis*information regarding this subject.

The bulk of the presentation constitutes a eulogy of Fisher, a famous mathematician, who has never done a blood-grouping test in his life. The central theme is Fisher's so-called synthesis, and on p. 34 appears the statement: "Fisher's predictions were soon confirmed, and the two antibodies having the reactions expected of them were apparently (sic!) discovered". Then follows the confession that the supposed discovery of anti-d was the result of faulty observations by impressionable, eager workers who had been over-anxious to be the first to prove Fisher right. On p. 35, with the faintest glimmer of insight, the author then writes: "The reader may feel he has been the victim of a deceit on that the whole argument has been built on the existence of d and the nature of its difference from D." On p. 15: "The antigen is no longer called the Rh factor," even though he uses the terms "Rh positive", "Rh negative", and "rhesus factor" throughout his pamphlet. Though hard to believe, this statement would imply that even dictionaries have been expurgated behind the CDE iron curtain.

The book contains the usual chapter on blood-groups and disease, quoting in extenso uncritical articles claiming associations between particular ABO groups and such diverse diseases as peptic ulcer, cancer of the stomach and lungs, diabetes, hypertension, &c. Surprisingly, the reports of certain workers who share the author's views are not quoted; for example, it is not clear why Buchwalter is not given full credit for his observations that group-A persons are prone to fracture of the femur.

The short bibliography at the end of the book is limited to books from behind the CDE iron curtain. None of my books are listed, which is fortunate for me, because books, like people, are sometimes judged by the company they keep.

With poetic justice, the fly-leaf of the book carries an amusing item by one of *The Lancet*'s peripatetic correspondents. Obviously, Roberts had no way of knowing who was the author of this piece, intended as a subtle satire of CDE paradoxers; for if he had known he would never have used it as the prelude to his "Odd" book.

New York. A. S. WIENER.

TRETAMINE IN THE TREATMENT OF INOPERABLE LUNG CANCER

SIR,—Following the preliminary communication by Mr. Jack and his colleagues,[1] we treated 7 patients with inoperable lung cancer in the manner they recommended.

The diagnosis was histologically proven to be anaplastic carcinoma in 6 patients and squamous-cell carcinoma in 1. Each patient was given tretamine 0·35 mg. per kg. body-weight intravenously as a single dose, preceded by 50 mg. of cyclizine ('Marzine') and 50 mg. pyridoxine intramuscularly. The immediate effects were mild, and no patient suffered more than slight nausea or occasional vomiting.

The effects of the tretamine on the blood were severe in most instances. The hæmoglobin level fell below 10 g. per 100 ml. in 5 patients. In 1 patient a level of 5 g. per 100 ml. was reached on the seventeenth day, despite repeated direct blood-transfusions.

In all patients the leucocyte count fell during the first week to reach a minimum level at about the twelfth day. In one patient this lowest level was 3000 per c.mm., in another it was 2000, and in the remaining 5 patients it was below 1000, despite the administration of prednisolone.

The blood-platelet levels in all patients fell to reach a minimum about the twelfth day. In one patient the minimum level was 180,000 per c.mm. The other 6 patients all reached levels below 25,000, despite the administration of prednisolone. Only 1 patient had purpura; another had small epistaxes.

In no patient was there any convincing radiological evidence of regression of the tumour. In most patients the radiological features became more extensive. 1 patient, who was bronchoscoped before treatment and again four weeks later, showed enlargement of the endobronchial portion of the tumour.

4 patients died of overwhelming infection between 15 and 32 days after the administration of tretamine, with leucocyte counts between 60 and 2000 per c.mm., despite the prednisolone, antibiotics, and barrier nursing.

The remaining 3 patients showed a slow rise of leucocyte and platelet counts after the fourth week. 2 of these patients, one of whom has the only squamous-cell tumour in the group, are now dying of malignant disease at 3 and 4 months respectively after treatment.

Only 1 patient remains clinically well 3 months after treatment, but, even in this instance, there is radiological and clinical evidence of progression of the tumour.

A review of these 7 patients shows:

(1) There has been no radiological or clinical evidence of regression of the tumour in any patient.

(2) There is no evidence that any patient has had his prognosis improved by the treatment.

(3) 4 patients died of overwhelming infection during treatment.

(4) The use of a large single dose of tretamine for the treatment of inoperable cancer of the lung is not to be recommended.

We wish to acknowledge the generous supply of tretamine and information by Imperial Chemical Industries Ltd.

Alfred Hospital,
Prahran,
Victoria, Australia. K. N. MORRIS
A. L. DAVIES.

1. Jack, D. J., Doyle, L., Palejwalla, M. M. *Lancet*, 1960, i, 207.

DOUBTFUL PROGRESS IN PSYCHIATRY

SIR,—To anyone who had experience in mental treatment even twenty years ago, Dr. Oliver's complaint (July 30) must seem extraordinary. And yet, not only other general practitioners but child psychiatrists will support him. Perhaps only the child psychiatrist sees all the havoc done to children who are obliged to live with a psychotic parent. Indeed, one of the consequences of getting the parents out of the mental hospital at any cost is to get their children into children's homes or schools for the maladjusted.

No-one, as Dr. Oliver says, wants the mentally sick to be imprisoned or forgotten—quite the contrary. What one deplores is that so often psychiatrists seem to cease to take responsibility for patients who are far from cured. Once a patient comes home from hospital, usually only "violence, sexual deviation, matricide" or the like gets him back again; though there may have been months of illness doing less spectacular damage.

It is perhaps right to say that patients who do not need or who cannot benefit further from medical care should not be in hospital. If, however, they are doing active harm to their families, they should not be at home. The answer presumably is hostels.

London, W.C.1. PORTIA HOLMAN.

THE HARVEST MITE

SIR,—Dr. Nelson's letter (July 16) is interesting. It is probably not generally known that the nymphs of these mites can live quite well on the house mouse (*Mus musculus* L.) which is really common outdoors on arable land,[1] being either the third commonest small mammal or even locally the most common.[2]

Until the drought of last year, house mice were extremely abundant all the year round in the open all over Skokholm Island off the Pembrokeshire coast,[3] and in 1957 I found harvest-mite nymphs commonly attached in large numbers to these mice. The typical sites of attachment were the external genitalia, in both sexes. In female mice, the mammæ were markedly delineated in red by the mites, and the vagina was sometimes actually occluded by them.

May it not be then, since your correspondent has noted that the local abundance of the mites is independent of whether rabbits have disappeared (or reappeared) or not, that *Mus musculus* is more important in the development of harvest mites than has hitherto been realised? There has been little systematic study of the ectoparasites of wild house mice living outdoors.

Infestation Control Laboratory,
Ministry of Agriculture, Fisheries and Food,
Surbiton, Surrey. R. A. DAVIS.

SIR,—Dr. Mellanby ended his letter of July 30 by saying "The man who says he is 'never bitten' may feed far more mosquitoes than the man who gives a severe reaction . . ." In my experience adults in rural areas are often immune to both weals and the irritation caused by local species of mosquito bites.

Many years ago when carrying out a mosquito survey at the Isle of Grain, in Kent (the most heavily mosquito-infested area I have encountered in England), I stood at the open doorway of a smallholding where the owner was hand-milking his cow, sitting on a stool with his forehead pressed against the ribs of the animal. I introduced myself and asked if I could search the shed for mosquitoes. His reply was a quite definite "you won't find any here but there are some down in the marshes". As he spoke I was looking at the back of his exposed neck and saw that it was covered with mosquitoes in the act of taking a blood meal.

At that time, 1918–20, more than half the children in the village, as well as many adults, had contracted malaria and in a house-to-house survey it was found that as many as a hundred mosquitoes (*Anopheles atroparvus*) could be found in a single bedroom.

I do not remember hearing a single complaint about mosquito bites from any of the residents, not even the children, and when I asked some of the parents if mosquitoes kept the children awake at night, the reply was invariably "Oh no, they be used to 'um".

Malaria Reference Laboratory,
Horton Hospital, Epsom, Surrey. P. G. SHUTE.

1. Southern, H. N., Laurie, E. M. O. *J. Anim. Ecol.* 1946, **15**, 134.
2. Davis, R. A. *The London Naturalist*, no. 35, June, 1956, p. 88.
3. Davis, R. A. Skokholm Island Observatory Reports, 1958, p. 26.

GROWING UP TODAY

SIR,—While pointing out the dramatic advance in the age of puberty in the last century, your good annotation of July 16 stated "not only has growth been speeded but the final sizes . . . are larger". The interesting thing about this phenomenon is that we apparently are not destined to become giants since, during the last century in different populations, final size has *not* increased greatly; the existing increase is out of all proportion to the great increase in growth rates *at various ages*. It is an occurrence, in the main, of earlier maturation; and so we stop growing earlier, too. Speculation as to causation is thereby made even more fascinating by this "division" of the phenomenon.

Child Development Unit,
University of Louisville Medical School,
Kentucky. FRANK FALKNER.

SULPHÆMOGLOBINÆMIA AND GLUTATHIONE

SIR,—Dr. McCutcheon's observations (July 30) are very interesting; but there are alternative explanations which seem to me no less likely, and these depend on factors which he seems to have neglected.

First, the methæmoglobin (M.H.) molecule is rapidly reduced to hæmoglobin (H.) by the glutathione system, and in patients where this mechanism is effective M.H. disappears from the blood within a few hours of withdrawing the drug which is responsible. The sulphæmoglobin (S.H.) molecule is much more stable, and persists for the duration of the life of the cell containing it. It follows that if, daily, 0·1% of the circulating H. be converted to S.H., then after 100 days or thereabouts equilibrium will be reached when the total H. will contain about 5% S.H. Since 0·1% of the circulating H. is approximately 2·5 g., and this quantity of S.H. can, in theory, be derived from only 1·5 mg. of hydrogen sulphide (H_2S), this is well within physiological possibilities.

Second, I showed [1] that constipation in itself had little or nothing to do with the development of sulphæmoglobinæmia due to drugs. The important factor was purgation, and Dr. Archer and I [2] were able to show that if patients were not purged, they did not develop S.H. It may be remembered that before the introduction of sulphonamides, the traditional treatment of infections involved purgation, often with castor oil, sometimes with calomel, more frequently with that nauseous concoction, black draught, of which an average dose contained 7 g. senna and 15 g. magnesium sulphate, so that after a few days excoriation of the anus added to the patient's sufferings. On this regime patients produced enormous volumes of nauseous flatus, containing not merely methane and hydrogen scented with indoles, but also large quantities of hydrogen sulphide, far more than is usual. Experiments on myself, using sulphur tablets, produced S.H. after three days, during which I became intermittently surrounded by an effluvium so rich in hydrogen sulphide that I had to take my meals in private.

Since then I have seen many patients with more or less intense sulphæmoglobinæmia; nearly all of them have been

1. Discombe, G. *Lancet*, 1937, i, 626.
2. Archer, H. E., G. Discombe, *ibid.* 1937, ii, 432.

women with chronic polyarthritis who regularly take some opening medicine, and constantly or intermittently take tab. codeine co. *B.P.* or some similar mixture containing phenacetin. The opening medicine varies, but is usually Epsom salt, Glauber salt, or some proprietary mixture containing these; in my last case, a week or so ago, it was ' Fynnon Salt '.

We know that in patients with favism the glucose-6-phosphate-dehydrogenase (G.6P.D.) and the reduced glutathione (G.S.H.) are normal shortly after recovery from a hæmolytic episode, but fall to much lower values after 40–60 days.[3] We also know that in patients with polyarthritis the life of the red cell is sometimes reduced by 20–30%. If the G.S.H. content of normal cells diminishes during their life span, though more slowly and less completely than does that of the abnormal red cell of G.6P.D. deficiency (favism), then one would expect patients with polyarthritis to show a distribution curve for red cell G.S.H. skewed somewhat to the right.

Since none of the figures Dr. McCutcheon gives are outside the range of normal established by Beutler,[4] it may be that his observed association between high G.S.H. levels and sulphæmoglobinæmia is due to chance; but I submit that the hypothesis outlined here is no less likely than that which he puts forward and, moreover, it is somewhat more amenable to experimental verification or contradiction.

Central Middlesex Hospital, London, N.W.10. GEORGE DISCOMBE.

PREVENTION AND TREATMENT OF BEDSORES

SIR,—Having used on my geriatric wards since November, 1959, a silicone aerosol spray of the composition described so clearly by Dr. Kelly (May 14) I now feel I can confirm his observations. One case stands out.

A 69-year-old woman with paraplegia in flexion, admitted in April, 1959, with a discharging sinus after various operations on a fractured femur, had multiple bedsores and urinary incontinence. Months of arduous nursing succeeded in maintaining life, but after twelve days' use of a trial supply of the spray a dramatic improvement of the bedsores was noted. Severe relapse followed exhaustion of the trial supply eight weeks later, but improvement was steady after a new supply was obtained. In particular the spray keeps the skin immune to irritation from urine. Since May she has been quite perky in a pleasant " convalescent " ward.

Many factors, of course, are involved; several expensive preparations have played their part, but the only two now in use are the spray and nursing care, which is, as Dr. Pathy (March 12) truly remarks, of paramount importance.

Summerfield Hospital, Birmingham. ROBERT J. HETHERINGTON.

EXTERNAL SPLINTAGE OF FRACTURES

SIR,—Dr. Robinson (Aug. 6) will be pleased to know that his logical solution has been tried out. Since external splintage plus muscle contractions tend to cause movement at the fracture site, one remedy is, as he says, deliberately to make the plaster case loose from the joint below downwards, and another remedy is to avoid exercises.

This " loose-below " plaster would also guard against another hazard of conventional treatment that I had not mentioned. The usual plaster case after a few weeks tends to become loose around the upper part of the limb, whilst remaining comparatively tight around the foot. This must result in much of the weight of the case being supported by the part of the limb distal to the fracture. The combined weights of distal part of limb and of the attached splintage seems to be a most undesirable load for the fracture to have to support.

I have put these conclusions into practice and for several years have used a " tight-above-loose-below " plaster and have banned physiotherapy. Of the 33 consecutive adult tibial shaft fractures so treated 32 united straightforwardly. Only 1 required a bone-graft.

It must be remembered, however, that the paradox concerns only the forces of internal origin. The effect of such a plaster against external forces is one of *lowered* efficiency. Therefore only a very uneasy compromise can ever be reached with external splintage in any form. It can be the treatment of choice only for the very mildest of tibial fractures—those that are highly likely to do well whatever the treatment. Something more efficient is required for the severe fractures such as are occurring in increasing numbers today.

Birmingham Accident Hospital. J. H. HICKS.

VASOPRESSIN AND BLEEDING ŒSOPHAGEAL VARICES

SIR,—During the past year we have been using intravenous vasopressin (' Pitressin ') as an adjunct to the control of hæmorrhage from œsophageal varices, and our experience agrees with that of Professor Sherlock and her colleagues (July 30).

Using our method of recording portal pressure [1] we have found that vasopressin will regularly lower portal venous pressure in man. The accompanying table illustrates the degree and duration of this action. The intestinal colic which also occurs, whilst distressing to the patient, has the advantage of emptying the bowel of blood and therefore helps to prevent the development of hepatic coma which is so often the sequel of a large gastro-œsophageal hæmorrhage in patients with cirrhosis of the liver.

Although by virtue of its constricting action on the arterioles and capillaries of the splanchnic bed and also on the intra-

QUANTITATIVE EFFECT OF VASOPRESSIN ON PORTAL PRESSURE

Patient	Condition	Dose of vasopressin (units)	Portal pressure (mm. water)		% fall	Duration of action (min.)
			Before	After		
1	Cirrhosis	10	330	190	42	15
2	,,	10	350	220	37	10
3	,,	10	350	210	40	15
4	After portacaval shunt	10	230	130	43	15
5	,,	5	250	150	40	14
6	,,	5	200	120	40	17
7	Thrombosed portal vein	10	230	130	43	8
8	,,	10	340	240	29	12
			Mean ..		39·1	13·6

hepatic communications between the portal vein and hepatic artery, vasopressin reduces the flow of blood into the liver, the drug may also, by raising the systemic arterial pressure, increase the flow through the hepatic artery itself, and hence to some extent compensate for the decreased flow through the other channels. We have been able to show this experimentally in the dog and cat, using a heated thermocouple needle as our measurement of changes in liver blood-flow, and we have also similar evidence for this occurrence in man.

Vasopressin is also useful during operations on the portal system when venous oozing obscures the operative field. For example we recently found that intravenous administration of the drug produced a relatively bloodless field for the surgeon during a difficult portacaval anastomosis. In a similar way we use the drug during the performance of portacaval anastomosis on normal animals in whom clamping the portal vein for half an hour results in congestion of the mesentery. Vasopressin prevents this. In exactly the same way the drug should be of value were one to resect the portal vein during operation for carcinoma of the head of the pancreas, and it might also be of use in reducing the flow of blood into the liver in severe liver injuries.

Department of Surgery, University of Bristol. CYRIL SHALDON.

3. Szeinberg, A., Sheba, Ch., Hirschorn, N., Bodonizi, E. *Bull. Res. Coun. Israel*, 1957, **6E**, 115.
4. Beutler, E. *J. Lab. clin. Med.* 1957, **49**, 84.
1. Shaldon, C. *Lancet*, July 30, 1960, p. 244.

THE SMELL OF "ACETONE"

SIR,—Professor Moncrieff (Aug. 6, p. 275) mentions that he cannot smell "acetone"; nor can I, although I have seen many cases of severe diabetic ketosis. However I can, and I am sure Professor Moncrieff can also, smell pure chemical acetone. It is clear therefore that what clinicians call "acetone" in the breath of patients with diabetic ketosis is not acetone. Is it acetoacetic acid, β-hydroxybutyric acid, or another substance not yet identified?

The subject is important, for many people think they can smell "acetone" and try to rely clinically on their alleged ability. In my experience about 50% of people cannot smell "acetone" and the fact should be generally realised.

Mayday Hospital,
Thornton Heath. G. P. BAKER.

ARTERIAL AUSCULTATION

SIR,—In the course of a much smaller experience I have found the systolic carotid bruit to be less specific than reported in your issue of July 30 by Professor Peart and Professor Rob, who state that they had never heard it in a case of complete internal-carotid occlusion. I have encountered this sign on four occasions in the presence of complete internal-carotid occlusion, in each case there being demonstrable stenosis of the *external* carotid. A further patient, with bilateral intermittent symptoms, had stenosis of the right internal and the left external carotid. The bruit was on the left. This is of more than theoretical interest, for if these patients had been operated on without angiography the results would have been disappointing and even hazardous. Regrettably, it seems that the stethoscope cannot replace the unpleasant and potentially dangerous carotid angiography in the accurate diagnosis of carotid-artery disease.

The Derbyshire Royal Infirmary,
Derby. W. B. MATTHEWS.

TISSUE THERAPY IN ANIMALS

SIR,—Tissue therapy was first tried in human beings by Filatov,[1] who made extensive tests with various tissues (homogenous and heterogenous); Troensegaard-Hansen [2] implanted human placenta in peripheral vascular disease; and Lahiri [3] reviewed the possibilities of tissue therapy and its application in India.

As far as I am aware, tissue therapy has never been tried in animal diseases. The trials recorded here were made on various species of domestic animals at the Bengal Veterinary College Hospital.

Skin was the only tissue used. Skins were obtained aseptically from live and recently dead animals (5 hours after death). They were immediately transferred to sterile petri dishes and kept at 4–5°C in a refrigerator. After 7 days they were removed and sterilised at 120°C for one hour. A 1-in.-deep skin incision was made in the diseased animal's chest wall behind the point of the elbow, and a pocket made by blunt dissection. 7 c.cm. of skin in small squares was introduced after removing the subcutaneous fat of the donor. The whole operation was done with all possible aseptic precautions.

The following were some of the conditions which were treated in this way:

(1) Hump sore in a bull (possibly stephanofilariasis): one implantation was given and a large sore disappeared within three months. Normal skin and hair grew on the affected area.

(2) Cutaneous rinderpest in a calf with concurrent coccidiosis. 80% of the nodules on the skin disappeared within 48 hours. The bloody stool due to coccidial infection became normal in colour after 72 hours. Dermatitis on the dewlap region assumed the normal colour of skin within 8 days.

(3) Buffalo with extensive skin lesions (exudative dermatitis). Oozing lesions became dry within 6 days. Cicatricial tissues appeared with progressive epithelialisation. Spotted pigmentation started covering the affected areas within 12 days.

(4) Cutaneous habronemiasis in a horse: a weeping granulomatous area dried up and cicatricial tissue appeared within 7 days. Sympathetic swelling of the joint above and below was considerably reduced by the 5th day.

(5) Non-specific eczema in a dog: the lesion dried up within 4 days and new skin appeared within 12 days.

(6) Follicular mange in a dog with extensive corrugated angry exudative lesion, extreme irritation on one side of the face including the external ear, and a widespread skin lesion. Much improvement within 3 days of implantation. Swelling in the mouth disappeared completely and oozing stopped.

A detailed account of this work will be published elsewhere.

Department of Veterinary Surgery,
Bengal Veterinary College,
Belgachia, Calcutta, India. D. K. RAY.

1. Filatov, V. P. Tissue Therapy. Moscow, 1955.
2. Troensegaard-Hansen, E. *Brit. med. J.* 1956, ii, 262.
3. Lahiri, S. C. *Antiseptic*, 1958, **55**, 833.

ABDOMINAL DECOMPRESSION IN LABOUR

SIR,—We were very interested to read Professor Heyns' comments (July 9) on our apparatus. I think he would agree with us that there are many ways of achieving abdominal decompression and the ideal method may not yet have been found.

May we take issue on some points that he raised? Firstly, we are still not quite sure from where Professor Heyns takes his pressure recordings. In published photographs of his apparatus the pressure-gauge is seen to be connected to the suction line. We measure our pressures with a completely separate tube leading from under the cage and submit that these must be the true pressure readings. If measured from the suction line, the pressures are very considerably lower than they are within the suit—e.g., a pressure of −100 mm. Hg is easily obtained in the suction line while the suit pressure is only −40 mm. Until we are sure what pressure is being measured, it is very difficult to draw comparisons.

The main reason for limiting patients to a maximum decompression of −50 mm. has been our experience that the abdomen is moved maximally (i.e., is touching the front of the cage as shown in our photograph) at around −40 mm., and increasing the negative pressure seems illogical. We would not stop the patient if she thought it helpful. We have used a back plate (which can easily be fitted to our cage) and find that although this stops the patient being lifted forward from the bed, the maximal abdominal movement still occurs at the same pressure—i.e., around −40 mm. Hg.

It has been said of our apparatus that most, if not all, the abdominal movement is due to this forward lifting of the patient (which is of course more marked in light patients). Our experiments with a back plate show that this is not so, but such a plate may have a place in patients of light build.

In all our experience so far we have never seen a bag burst, in spite of pressures up to −80 mm. Hg being used. This we attribute to the fact that no large area of polyethylene is left unsupported when the patient is in position (it is quite easy to burst bags experimentally at −30 mm. Hg if large areas are allowed to bulge). Moreover we have taken especial care to ensure smooth surfaces in our cages and to see that the bag is not damaged during the setting up of the patient within the apparatus. The bandage seal round the thighs is tied only lightly and certainly does not cause venous congestion.

We find Professor Heyns' ideas on the nature of the pain of labour very interesting and feel sure that more work on the effects of abdominal decompression will elucidate some aspects of this difficult problem.

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and Gynæcology,
University of Edinburgh. D. B. SCOTT
J. D. O. LOUDON.

TOXIC EFFECTS OF PROLONGED TREATMENT WITH FURALTADONE

SIR,—A new systemic chemotherapeutic agent furaltadone ('Altafur') has recently become available. A synthetic nitrofuran with the formula 3-(5-nitro-2-furfuryl-ideneamino)-5-(4-morpholinomethyl)-2 oxazolodine, it is effective against gram-positive cocci, *Escherichia coli*, most salmonellæ, and some other microorganisms,[1] but its particular value is against staphylococci which have become resistant to the common antibiotics.

Loftus and Wagner[2] have described two examples of double vision associated with furaltadone therapy. In one case the diplopia appeared after 10 weeks, when the patient had had a total dose of 68 g. furaltadone; in the other the exact onset of diplopia was uncertain.

Apart from this account significant toxic effects have not been described; hence I should like to report four patients who have had severe toxic symptoms and signs during prolonged treatment with furaltadone.

CASE 1.—A man, aged 39, sustained a severe compound fracture of the right tibia and fibula on June 17, 1959. The wounds were cleaned, excised, and sutured, and the limb was immobilised in a plaster cast. He had mild but continuous fever for 2 weeks, and was given a course of systemic penicillin therapy. On the 14th day the wounds had all healed except for a persistent discharging sinus from which, on Oct. 16, *Staphylococcus aureus*, resistant to penicillin and chlortetracycline, was cultured. On Dec. 8 furaltadone 250 mg. q.d.s. was started. On Feb. 1, 1960, he complained of double vision for distant objects (after a total of 66 g. of furaltadone). The drug was discontinued, and the patient was given a course of vitamin-B complex. He was seen at that time by an ophthalmologist, who found a left lateral-rectus palsy. No other ocular or nervous abnormality was found. The diplopia gradually recovered, and by Feb. 14 it had entirely disappeared, leaving no residual abnormality. This patient had no previous history of sensitivity to any chemotherapeutic agent.

CASE 2.—A girl, aged 8 years, had an operation on Dec. 4 for a Brodie's abscess of the lower end of the left tibia which had caused symptoms for 8 months. The abscess cavity was evacuated, and from it was cultured *Staph. aureus* which was resistant to penicillin but sensitive to erythromycin. She was therefore given erythromycin 200 mg. t.d.s. for 10 days. On July 1, 1959, a further operation was necessary for recurrence of the abscess, and on Nov. 12 a subcutaneous abscess required drainage. *Staph. aureus* with the same sensitivity was cultured each time, and over both these recurrences the child was given 14-day courses of erythromycin 250 mg. 6 hourly. After the last operation a sinus developed from which was cultured the same *Staph. aureus*.

On Dec. 14 the child began to take furaltadone 500 mg. daily (19 mg. per kg. body-weight) in divided doses. On Feb. 2, 1960, the dose was increased to 750 mg. daily (28 mg. per kg. body-weight). On Feb. 5 (when a total of 22 g. furaltadone had been taken) she complained of diplopia when looking at distant objects to her right. She had right lateral-rectus weakness, and nystagmus when looking to the right. Furaltadone was reduced to 500 mg. daily, and after 2 days the diplopia for distant objects ceased. On Feb. 18 her voice became deeper and rather husky, and she had difficulty in swallowing solids. Normally an alert child, she became lethargic and depressed; she did not concentrate, and her school work deteriorated. She also developed physical affection for the nursing staff and other girls in the ward. On Feb. 23 furaltadone was discontinued, a total of 31 g. having been given. After a further week of mental deterioration she began to recover, and by March 21 her voice, behaviour, and school work were normal. She had no history of previous sensitivity to any chemotherapeutic agent.

CASE 3.—A man of 42, was admitted to hospital on April 30, 1957, with a pyogenic infection of the lumbosacral region of his spine. He was immobilised in a plaster bed, and for several months was given short courses of chlortetracycline 1 g. daily and erythromycin 1 g. daily.

On Aug. 13 a pelvic abscess was drained surgically, and from this was cultured *Staph. aureus* which was resistant to penicillin but sensitive to erythromycin and streptomycin. Afterwards a sinus persisted in the abdominal wall.

In March, 1958, the sinus became secondarily infected with *Proteus vulgaris* which was sensitive to streptomycin. On March. 12 treatment was started with streptomycin 1 g. daily by injection. On May 9 streptomycin was discontinued (after a total of 60 g. had been given) because the patient had become dizzy. Further streptomycin was given in November and in April, 1959, without recurrence of the dizziness. But the sinus continued to discharge, and on Dec. 28 treatment was started with furaltadone 1 g. daily (in four divided doses).

On Feb. 1, 1960, the patient complained of a "swimming feeling" in his head, and on Feb. 10 (after a total of 44 g. furaltadone) he had persistent slight dizziness and diplopia for distant objects. This became gradually worse until the furaltadone was discontinued on Feb. 22 (after a total dose of 56 g.) and he was given vitamin-B complex. When he attended the outpatient department on March 7 he no longer had diplopia and his ocular movements were normal, but he was still somewhat dizzy.

CASE 4.—A man of 22, had intermittent discharge from a sinus in the lower part of the left thigh. In 1947 he had been treated with penicillin alone for an acute hæmatogenous osteomyelitis of the shaft of the left femur. In 1950 a recurrence of this osteomyelitis responded to simple rest in bed.

A culture from the sinus grew *Staph. aureus* sensitive to penicillin. Penicillin was given intramuscularly before operation but unfortunately he soon became allergic to it. On Nov. 28 treatment with furaltadone 1 g. daily (in four divided doses) was started. This was discontinued on March 8, 1960, because previous experience suggested that he too might develop toxic symptoms. The total dose of furaltadone was 101 g. From Feb. 2 to 16 he was also given tetracycline 1 g. daily. It was later discovered that he had complained to the nursing staff of double vision 10 days before the furaltadone was discontinued, and that this persisted for 21 days. When examined, the diplopia had already ceased, and no ocular abnormality was detected.

In these four patients diplopia appeared after 7–14 weeks' treatment with furaltadone. It was due to external-rectus weakness in cases 1 and 2, and similar paresis may reasonably be presumed in the other two cases. The second patient also had difficulty in swallowing solids, an alteration of voice, and personality changes, suggesting that the toxic changes were central rather than peripheral, and that several cranial nuclei were involved and possibly also the prefrontal region of the cerebral hemispheres.

Certain nitrofuran compounds inhibit pyruvate dissimilation in bacterial cell-free extracts.[3] Nitrofuran compounds affect the ability of the rat testis to form citrate from oxalacetate, this effect ceasing within a week of stopping the drug, though citrate synthesis by brain tissue was not affected by the dosage used.[4] Possibly prolonged administration of furaltadone affects the carbohydrate metabolism of these cranial-nerve nuclei.

Although case 3 was treated with tetracycline as well as furaltadone, there is no reason to believe that it was responsible for the development of diplopia. The dizziness that developed with streptomycin therapy may indicate a tendency to drug allergy in this patient, who alone complained of dizziness shortly before diplopia

1. Kefauver, D. F., Paberz, I., McNamara, T. F. *Antibiotics Annu.* 1959, p. 81.
2. Loftus, R. L., Wagner, A. W. *J. Amer. med. Ass.* 1960, **173**, 362.
3. Asnis, R. E., Glick, M. C., Fritz, M. *Brit. med. J.* 1957, ii, 863.
4. Paul, H. E., Paul, M. F., Kopko, F., Bender, R. C., Everett, G. *Endocrinology*, 1953, **53**, 585.

appeared. The only common factor in the treatment of these four patients was the prolonged administration of furaltadone, which seems to have caused the toxic symptoms and signs. This suggests that treatment with furaltadone should not be continued for more than 6 weeks.

I wish to thank Prof. J. Trueta and Mr. J. C. Scott for their advice and criticism and for permission to report cases 1, 2, and 4; Mr. J. D. Morgan for permission to report case 3; and Mr. J. W. Goodfellow who kindly supplied details of case 1.

Nuffield Department of Orthopædic Surgery, Oxford. M. L. H. LEE.

SNAKEBITE

SIR,—Dr. Penman (June 25), in suggesting "snakebite" as a specific word for snakebite poisoning, seems to assume that bites from poisonous snakes inevitably entail poisoning. This is a serious error, responsible for much of the confusion regarding snakebite. In 517 cases of snakebite victims personally observed in hospital during the last $2^1/_2$ years, the snake was reliably identified as poisonous in 324 bites (pit vipers 283, cobra 13, coral snake 2, sea snake 26). No poisoning followed 78 (25%) of these 324 bites: in 98 (30%) only trivial poisoning ensued. It is most important that clinicians should realise poisonous snakebite is *not* synonymous with snakebite poisoning.

In 22 of these 517 cases, the snake was non-poisonous. Dr. Penman would have difficulty in finding a similar number of manbites in dogs.

General Hospital, Penang, Malaya. H. A. REID.

TRIAL OF A NON-SPECIFIC ANTI-CATARRH VACCINE

SIR,—May I be permitted to comment on the letter of Dr. Clark and Dr. Grenville-Mathers (June 25)? To my mind a very small alteration in their table II (response to treatment) would permit a very different conclusion.

I suggest it would be more reasonable to bracket "good result" and "moderate improvement" together, rather than "moderate improvement" and "stationary". This change would show some degree of improvement in 7 out of 15 controls (46·79%) and in 50 out of 79 (63·33%) in treated cases. Surely the efficacy or otherwise of the course of injections depends on the presence or absence in the vaccine of the organism or organisms to which the patient is particularly sensitive? In the absence of the particular organism the vaccine is no more than the equivalent of the distilled water used on the controls. Furthermore, surely it is hardly permissible, statistically, to compare results in 15 and 79 cases.

For the immunisation of patients who are particularly susceptible to colds, it has been for some years my custom to use a non-specific vaccine prepared by the South African Institute for Medical Research which contains:

Streptococcus pneumoniæ	300	million per ml.
Strep. pyogenes	300	,, ,,
Klebsiella pneumoniæ	300	,, ,,
Staphylococcus aureus	300	,, ,,
Hæmophilus influenzæ	150	,, ,,
Neisseria catarrhalis	150	,, ,,

According to the instructions issued with the vaccine, a course of injections commencing with 0·1 ml. and increasing, according to the reaction, to 2 ml. is given hypodermically. The next injection is not given until the reaction to the previous one, both local and general, has subsided, usually from two to three days. The average course is ten injections. If the course begins early in the "cold season" a booster of 1 ml. is given after three months, otherwise it is given at the end of the season. At the beginning of the following season 1 ml. and 2 ml. doses are given.

Though no control series is possible in general practice, it is remarkable how regularly the immunees return for their booster doses. As this may be six to nine months after the original course, it is reasonable to assume that the "psychological" boost is negligible. On one or two occasions it was noted that the local and general reactions to the booster dose was greatly in excess of that experienced during the original course. In such cases boosters of 0·5 ml. and 1 ml. were administered.

Where no reaction followed a rapid increase in dosage during the initial course, I have assumed that the particular organism to which the patient is sensitive is missing from the vaccine and have, where possible, substituted an autogenous vaccine.

From the patient's point of view it is a matter of luck whether his particular organism is present or not. If it is, the immunisation is successful: if it is absent there is no immunity. It is as simple as that.

Hill Crest, Natal. PHILIP H. DALGLEISH.

FAILURE TO DEMONSTRATE POLIOVIRUS-NEUTRALISING ANTIBODIES IN STOOLS

SIR,—In a preliminary communication Steigman and Lipton [1] reported that poliovirus-neutralising antibodies had been demonstrated in stool specimens from children with paralytic or aparalytic poliomyelitis. The fæcal specimens were prepared as 20% suspensions and examined by neutralisation tests in tissue culture after heating the stool suspensions at 56°C. Steigman and Lipton emphasised the desirability of other investigators attempting to confirm these findings. Consequently 42 stool specimens from patients with paralytic poliomyelitis have been examined in our laboratory for the presence of polio-neutralising antibodies.

Fæcal specimens examined.—42 stool specimens from 13 patients with a clinical diagnosis of paralytic poliomyelitis had previously (September, 1958, to July, 1959) been examined by the routine method used in our laboratory.[2] All 13 patients were found to excrete poliovirus (type I or III) during the acute phase of illness. The stools were kept as 10% suspensions at −20°C until the present testing for neutralising antibodies in February and March, 1960.

From 3 patients, aged 1, 4, and 16 years, series of fourteen, six, and nine stool specimens, respectively, collected during the acute and convalescent illness, were examined (experiments 1, 2, and 3 in the accompanying table). Thirteen samples from 10 patients had been collected from 9 to 38 days after onset of illness (experiment 4).

POLIO-NEUTRALISING ANTIBODIES IN STOOLS OF PATIENTS WITH PARALYTIC POLIOMYELITIS

Expt.	Doses of poliovirus in neutralisation tests			No. of stools		Stool controls		Illness caused by poliovirus type
	I	II	III	Examined	With demonstrable antibodies	Negative	Toxic	
1	120	40	120	14	0	14	1	III
2	50	10	8	9	0	9	0	III
3	120	100	120	6	0	6	1	I
4	80	25	80	13	0	13	2	I or III

Technique.—The 10% stool suspensions were thawed and mixed with equal amounts of saline (making a final dilution of 1/20), and then placed in a waterbath for 1 hour at 56°C. The stool suspensions were distributed to four tubes, each tube receiving 0·25 ml. To three of the tubes 0·25 ml. of poliovirus type I, II, or III was added. The fourth tube received 0·25 ml. of saline. This latter mixture served as control for (1) adequate

1. Steigman, A. J., Lipton, M. M. *Lancet*, 1959, ii, 272.
2. Godtfredsen, A., von Magnus, H. *Dan. med. Bull.* 1959, **6**, 264.

inactivation of virus present in the stool suspension, and (2) toxic effect exhibited by the stool suspension. After incubation for 1 hour at room temperature, 0·2 ml. of each mixture was inoculated into two roller tubes with trypsinised monkey-kidney cells containing 1·8 ml. of Medium 199. Simultaneous titration of poliovirus types I, II, and III was carried out in each experiment. After inoculation the tissue-culture tubes were placed in roller drums and examined for cytopathic lesions 3 and 7 days after inoculation.

Results.—As will be seen from the table, neutralising antibodies against poliovirus could not be demonstrated by the technique employed in any of the forty-two specimens examined—i.e., all specimens had a "titre" less than 1/40. In 4 cases the stool suspensions exhibited slight toxic effect but not to a degree which prevented reading of the neutralisation test.

The findings by Steigman and Lipton of neutralising antibody titres of 1/80 or more in stool specimens could thus not be confirmed in our laboratory. The stool suspensions examined here had been stored for a rather long time at −20°C before tested. It seems, however, unlikely that this storage should have any destructive influence on neutralising antibodies.

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State Serum Institute,
Copenhagen. ANNELISE GODTFREDSEN.

CONTROL OF MICTURITION

SIR,—I find, as others may, some entertainment and instruction in the fact that while in the current issue of *The Lancet* there is an article by Mr. S. A. Vincent on the mechanical control of urinary incontinence by means of an inflatable bag so arranged as to press upon the anal and perineal regions, there is in the current issue of *Encounter* an article by Mr. Arthur Koestler describing a Hatha Yoga technique called the *Maha Bandha*, or "Great Binding", for control of the anal and urethral canals through perineal pressure by the heel of the left foot. This well-conceived disposition of the left foot is an integral part of the classic Lotus Posture adopted by Oriental contemplatives for the past thousand years, and perhaps much longer.

As well as providing an elegant illustration of the general truth that most discoveries are re-discoveries, the conjunction of these two observations affords room for our delighted recognition of a neat and unobtrusive answer to one of the perennial hindrances to middle-aged meditations.

London, W.1. ALAN MCGLASHAN.

STARCH-GEL ELECTROPHORESIS OF LEUKÆMIC SERA

SIR,—A recent publication[1] from this laboratory seemed to indicate the possibility that there was a preponderance of haptoglobin group 1–1[2] in sera from patients with chronic leukæmia, with special reference to chronic lymphatic leukæmia.

Realising the possible importance of this finding we have examined leukæmia sera from 27 patients by means of the more sensitive vertical starch-gel electrophoresis technique.[3] The group contained 20 individuals with chronic lymphatic leukæmia. 6 of these had been included in the previous investigation.[1] The distribution of the serum-haptoglobin grouping has not been significantly different from normal and we can only conclude that this further investigation has shown no apparent connection between the haptoglobin grouping and chronic leukæmia of any kind.

We are, however, still finding interesting abnormal protein patterns after starch-gel electrophoresis of certain sera from leukæmic patients. We are proposing to investigate these further by using immunological techniques.

Department of Pathology,
Royal Victoria Infirmary,
Newcastle upon Tyne. A. L. LATNER
A. W. SKILLEN.

1. Latner, A. L., Zaki, A. H. *Clin. chim. acta*, 1960, **5**, 22.
2. Smithies, O., Walker, N. F. *Nature, Lond.* 1956, **178**, 694.
3. Smithies, O. *Biochem. J.* 1959, **71**, 585.

COMPLETE REMISSION OF STEVENS-JOHNSON SYNDROME AFTER STEROID THERAPY

SIR,—In the following case of severe Stevens-Johnson syndrome steroid therapy was associated with a complete remission.

A 17-year-old Puerto Rican male was admitted to this hospital because he had had fever and cough with expectoration for about a week. Before admission he had been treated with penicillin, and later sulphadimethoxine, novobiocin ('Panalba') ('Madribon'), and tetracycline, without response. His condition rapidly deteriorated. On admission he had high fever, sore throat, cough with expectoration but no hæmoptysis, general malaise, and soreness and ulceration in the mouth. He looked dehydrated and very ill. The temperature was 106°F, blood-pressure 110/70 mm. Hg., pulse 110 per min. and regular, respirations 26 per min. There was no skin rash or petechiæ. The conjunctivæ were injected, but the eyes were otherwise normal. There was severe stomatitis with ulcers of the palate, cheek, and mucocutaneous junction. The pharynx was injected but did not contain exudate. Examination of the chest and lungs was unremarkable except for diffuse wheezes and rhonchi at the right base posteriorly. There was no evidence of cardiac enlargement and no murmurs or gallop. There were no other significant clinical findings. The initial impression was that of pneumonia of the right lower lobe.

He was given large doses of penicillin and chloramphenicol, and aspirin to control the fever. Several cultures were taken before antibiotics were given. Serial chest films were normal. The urine contained a trace of albumin. The hæmoglobin was 14·5 g. per 100 ml., white cells 10,800 (with 78% polymorphs, 19% lymphocytes, 3% eosinophils). The erythrocyte-sedimentation rate was 56 mm. in the first hour (Westergren). Serological tests were negative, and blood constituents were within normal limits. The cold-agglutinin titre was negative.

A hectic temperature persisted and the stomatitis became worse. Since this was assumed to be due to the antibiotics, he was given an antifungal agent, nystatin ('Nycostatin'), in full doses. There was now a severe hæmorrhagic conjunctivitis, photophobia, and questionable iritis. The eyes appeared swollen and the face was flushed. Some of the mouth lesions began to bleed. On the third hospital day there was questionable neck rigidity, and spinal tap was performed: the initial pressure was raised, but the contents of the fluid were within normal limits. Blood-cultures and C.S.F. cultures were negative. Cultures of the throat and sputum showed several unrelated pathogens, and urine culture grew a non-hæmolytic *Staphylococcus aureus* and *Aerobacter aerogenes*.

On the fourth hospital day he had severe conjunctivitis with iritis, photophobia, ulcerative hæmorrhagic stomatitis, erythematous eruptions of the scrotum, urethritis, and dysuria. The skin lesions were at first macular, later becoming vesicular and then rupturing to produce weeping lesions. The lesions of the buccal mucosa and lips became intensely hæmorrhagic and diffusely encrusted, resembling a superficial but diffuse clot engrafted upon weeping ulceration.

The diagnosis of Stevens-Johnson syndrome was made and he was immediately given 300 mg. of hydrocortisone by continuous infusions daily. The lesions were soaked with warm saline, and 'Neo-Cortef' ophthalmic ointment and homatropine drops were instilled into the eyes several times daily. All antibiotics were discontinued except tetracycline, which was used to prevent a secondary infection.

He responded dramatically. The temperature dropped significantly, he became much less toxic, and the lesions of the eyes, mouth, scrotum, and urethra started healing with crust formation. He was able to eat again. Steroids were gradually reduced to 30 mg. of prednisone daily and thereafter, after tapering, were completely discontinued. The skin and mucous membrane lesions gradually cleared, his appetite returned, and he started to gain weight. He was discharged four weeks after admission and so far he remains in complete remission.

We thank Dr. Michael S. Bruno, director of the department of medicine, Knickerbocker Hospital, for his guidance in writing this report.

Department of Medicine, Knickerbocker Hospital, New York City. FURMAN M. JONES, Jr. P. NARASIMHAN.

ANÆSTHETIC MACHINES

Dr. J. G. BOURNE writes: "The Treasurer of St. Bartholomew's Hospital has asked me to make known through your columns that the tests referred to on pp. 132 and 164 of my book, *Nitrous Oxide in Dentistry*, were made in March, 1956, and that the machines at present in use at that hospital have been tested by the head of the Department of Anæsthesia and are functioning satisfactorily."

EPIDEMIC NEPHRITIS IN NORTH ESSEX

Dr. JOHN HARKNESS writes: "My article of July 11 contained no acknowledgment to the pathologists who carried out the laboratory work. Owing to a most unfortunate oversight, this acknowledgment was omitted from the final draft of the paper. The work was done by Dr. R. Pilsworth, Public Health Laboratory, Chelmsford, and Dr. J. B. Penfold, Essex County Hospital, Colchester, and the streptococcal typing was done at the Central Public Health Laboratory, Colindale. I apologise to these pathologists and to the readers of your journal."

Public Health

Progress of Smoke Control

IN January of last year the Minister of Housing and Local Government asked each local authority in the "black" areas, where air pollution is worst, to submit programmes showing its plans for smoke control up to 1963, and the year by which it hopes to finish the job. A summary of these programmes has now been issued.[1]

By the end of 1958 some 120,000 premises and 17,000 acres in the black areas were covered by smokeless zones or smoke-control orders. Estimated progress this year (470,000 premises and 111,000 acres) is about double that estimated for last year. The programmes envisage that something like this rate will be maintained in each year up to 1963; and, if so, some $2^1/_4$ million premises (including 2 million houses) and nearly half a million acres should then be smoke-controlled. This would be almost half-way towards the final objective of the authorities which have submitted programmes. But information about the rate of progress by local authorities in 1959 shows that this fell a good deal short of what had been planned.

The dates set for the completion of local-authority programmes range from 1962 onwards. The County of London, it is estimated, will be largely smoke-controlled by 1975.

A provisional list made by the Ministry shows that the areas of 294 local authorities in England, and 30 in Wales, may be regarded as wholly or partly black. By the end of March, 85 of the English authorities had not submitted programmes, and only 1 of the 30 Welsh ones had done so. The commonest reasons were that the authorities did not agree that their districts were black (the Welsh response to the circular "probably reflects the relative smokelessness of much of the house coal used in Wales and Monmouthshire"), or that they were concerned about the effect of smoke-control orders on people entitled to receive coal at concessionary prices. Most of the rest said that they had not yet been able to prepare a programme, or that they wanted to proceed with a pilot scheme before doing so.

1. Smoke Control (England and Wales): Summary of programmes submitted by local authorities. Cmnd. 1113. H.M. Stationery Office, 1960. Pp. 19. 3s.

Morbidity Statistics from General Practice

The General Register Office published last week the second volume of *Morbidity Statistics from General Practice*.[1] The first volume described the methods and tabulated the general statistical results of the survey, presenting both the amount of sickness for which patients consulted their doctors and its distribution by sex, age, and area. The second volume deals with the distribution among men, women, and children of sickness by occupation and social class, presenting the results of a study of some 280,000 clinical records of over a hundred general practitioners in England and Wales. It is based on a year's survey (May, 1955, to April, 1956) carried out by the College of General Practitioners and the General Register Office.

The occupations of all patients, whether or not they consulted their doctors during the survey year, were recorded, thus providing the total number of patients "at risk" in each occupational group, to which sickness could be related and on which rates could be calculated. The basic information is given in a series of tables showing the distribution of sickness by occupation, sex, age-group, and geographical area.

Men

For men aged 15 to 64, a series of ratios based on selected diagnoses by social class and occupation were calculated (the ratio for all occupations is 100), and these ratios give a measure of comparative morbidity in the various social and occupational groups. They do not compare numbers of consultations but numbers of persons in each occupational group who consulted their doctor for the stated condition.

For all diagnoses, faceworkers in mines had a ratio of 124 (24% above average) and farmers and other agricultural workers had the lowest ratios—81 and 80 respectively.

Psychoneurotic disorders.—Farmers (48) and other agricultural workers (61) had low ratios; professional and administrative workers (123), clerks (133), and foremen (127) had high ratios.

Coronary disease.—Groups with high ratios were shopkeepers (144), clerical workers (139), and foremen (135); and groups with low ratios were mineworkers (32), agricultural workers (39), and farmers (58).

High blood-pressure.—There were higher than average ratios of 120 and 127 in social classes I and II (professional and administrative), lower than average ratios of 70 and 89 in social classes IV and V (semi-skilled and unskilled). The group with the highest ratio was personal service (147). Shopkeepers (134) contrasted with shop assistants (69). Agricultural workers (52) and mineworkers (62) were lowest.

Common cold.—Mineworkers had a ratio of 288, almost three times the average for all men. All the manual groups and in addition clerical workers were above average. Groups with low ratios were farmers (58) and shopkeepers (66).

Bronchitis.—Of all the diagnoses listed this gave the steepest social class gradient, rising from 49 in social class I (professional) to 146 in social class V (unskilled)—a distribution similar to that associated with mortality. Low ratios were recorded for farmers (70) and other agricultural workers (60), the two professional and administrative groups (49 and 70), shopkeepers (73), and shop assistants (73). Semi-skilled and unskilled manual workers on the other hand had ratios of 152 and 146, and mineworkers 210.

Gastric and duodenal ulcer.—There was a steep and almost regular ascending gradient from social class I (48) to V (116). Groups with low ratios were farmers (58), agricultural workers (62), higher professional, &c. (48), and shop assistants (67). All the manual groups had ratios above average, particularly foremen (136) and transport workers (139).

Arthritis and rheumatism.—There was a distinct and almost regular social-class gradient, rising from social class I (58) to social classes IV (115) and V (111). The ratio for mineworkers was 309—three times as many men in this occupational group consulted their doctor for rheumatism as did the general male population. Ratios were low for

1. Studies on Medical and Population Subjects no. 14: Morbidity Statistics from General Practice, Vol. II (Occupation). H.M. Stationery Office. Pp. 269. 25s.

farmers (77), agricultural workers (70), professional and administrative (58 and 71), and shopkeepers (70), high for the manual groups, particularly the semi-skilled (148).

Women

No distinction was made between married and single women, and all the women included in the survey were classified by their own occupation, if they had one, and by their occupational category—i.e., working full or part-time, and with or without family responsibilities. Married women were classed as housewives only if they had no other full-time or part-time occupation.

For all diagnoses, the rates for housewives were slightly below the average for all women. Women working full-time who look after a home and family in addition had a consultation rate 31% above average, and women working part-time, whether or not they have family responsibilities, had a consultation rate of 22% above average.

For each of the following diagnoses the proportion of patients aged 15–64 consulting their doctor was highest for women working full-time who also had family responsibilities: psychoneuroses, common cold, bronchitis, disorders of menstruation, and arthritis and rheumatism (except rheumatic fever). At ages 65 and over housewives had higher rates than women in the two other categories for "all diagnoses" and also for bronchitis and for arthritis and rheumatism.

Infectious Diseases in England and Wales

Disease	Week ended July				
	2	9	16	23	30*
Diphtheria	2	3	2	8	...
Dysentery	706	615	639	592	566
Encephalitis:					
Infective	3	6	6	7	2
Postinfectious	3	4	3	1	2
Food-poisoning	241	218	248	255	222
Measles, excluding rubella	2674	2511	2703	2692	2856
Meningococcal infection	19	23	18	21	17
Ophthalmia neonatorum	20	20	27	15	21
Paratyphoid fever	4	7	1	11	12
Pneumonia, primary or influenzal	145	147	145	152	131
Poliomyelitis:					
Paralytic	13	7	5	6	7
Non-paralytic	5	9	11	10	9
Puerperal pyrexia	158	148	197	188	173
Scarlet fever	378	406	422	451	429
Smallpox	..	..	..	..	..
Tuberculosis:					
Respiratory	397	440	423	435	409
Meninges and C.N.S.	5	4	4	5	7
Other	50	59	52	71	58
Typhoid fever	2	...	3	5	2
Whooping-cough	1781	1619	1628	1602	1389

* Not including late returns.

Obituary

THOMAS GILLMAN MOORHEAD

M.D. Dubl., LL.D., F.R.C.P.I., F.R.C.P., D.P.H.

Dr. Moorhead, formerly president of the Royal College of Physicians of Ireland, and president of the British Medical Association in 1933, died on August 3 at the age of 82.

The son of Dr. W. R. Moorhead of Bray, Co. Wicklow, he qualified at Trinity College in 1901, and was appointed visiting physician to the Royal City of Dublin Hospital only two years later. He rapidly won a reputation as a clinical teacher of outstanding merit. During the 1914-18 war he served for a time with the R.A.M.C., in which he was a lieutenant-colonel. His practice grew and grew, and he was soon the leading consultant in Dublin. In 1921 he became King's professor of materia medica at Trinity College, and moved to Sir Patrick Dun's Hospital. A few years later the blow fell, and, as a friend puts it, "this Samson of Dublin medicine became blind". His career as a teacher and as a consultant was at an end. He resigned from the chair of materia medica and he gave up his hospital work. But his strength of mind and his strength of body were unimpaired, and he found new outlets for his immense energy. He became regius professor of physic and held this post for the next thirty years. Honours and work crowded on him. Besides the College of Physicians and the B.M.A., he was president of the Association of Physicians of Great Britain and Ireland, and served on the General Medical Council, the board of Trinity College, and the boards of Sir Patrick Dun's Hospital and Newcastle Sanatorium—to mention only some of his activities. His honours included the degree of doctor of laws from the National University of Ireland and from the Queen's University, Belfast, and election to the fellowship of the Royal College of Physicians of London under the special by-law in 1939.

For the following tribute we are indebted to V. M. S.:

"The news of Moorhead's death will awaken memories in many ageing medical men in many lands, who had the good fortune to sit at his feet when he was at the height of his clinical powers—perhaps one should rather say to stand packed close together or peering over someone else's shoulder, for the crowd was immense and students were attracted to his clinical lectures from all the other Dublin hospitals.

"Punctually on the stroke of 9 he appeared—the erect, rather small man, with the close-cropped dolichocephalic head, the small bristling moustache, the big spectacles, and the long well-starched white coat. The resident gave the history. The important physical signs were demonstrated. A few deft strokes of the grease pencil outlined the enlarged liver and the dull area at the base of one lung. One or two lucky students were given the opportunity of confirming the findings. What was wrong with the patient? The evidence was weighed. The only three possible reasonable diagnoses were written on the blackboard in the order of their probability. The X-ray was strongly in favour of no. 3. Laboratory results were confirmatory. Here was a case where clinical features alone might have misled one. What should be done? What was the patient told?

"As we filed out, what were our thoughts? Medicine is really quite simple; it is a most interesting subject; physical signs are very important, but they must be checked by whatever other methods are available; how clearly he puts everything—we'll certainly come to hear Tommy Moorhead again. And years afterwards when our patient says 'Thank you so much, doctor, for your good examination; I've never been examined so thoroughly before, and I'm quite satisfied now that there is nothing really wrong with me,' we say under our breath, 'Don't thank me, thank Dr. Moorhead."

"Moorhead was a man of method and precision. In his heyday he rose at 6 A.M. 7 A.M. found him at the private nursing-home. He worked there till 9 A.M., and then at hospital for some hours, with probably a consultation in the suburbs before lunch. All the afternoon he had consultations at his house, then more consultations outside. After dinner perhaps a medical meeting, or reading the journals, or writing up an unusual case for publication. Saturday afternoon some fresh air, with perhaps a theatre in the evening. And so it went on—not to mention the many country consultations which might encroach on his timetable or cut down his hours of sleep. He was the perfect efficient human machine. It was overhauled by six weeks' holidays in the summer—three weeks abroad, perhaps mountain-climbing, and three weeks in the west of Ireland fishing. And so the years went on until the crash came.

"After he became blind it was obvious what a prodigious memory Moorhead had. He could make a long and excellent speech without a note. He could remember exactly what was said at a meeting. Medical books and journals were read out to him, and, though he was the first to recognise his own limitations, he had a considerable grasp of the advances which were taking place so rapidly in medicine.

"As the years passed he mellowed and was probably really much happier than during the years of his greatness when he was the slave of the clock. He bore his long final illness with patience and courage, sustained by the loving care of his wife."

Mrs. Moorhead, whom he married in 1938, is the daughter of the late Stephen Gwynn. His first marriage was in 1907, to M. B. Quinn.

Notes and News

PRESCRIBERS' NOTES

THE Ministry of Health and the Department of Health for Scotland have decided to extend the scope and the content of the existing publication *Prescribers' Notes* (which is sent to all doctors in the National Health Service) to give doctors more information about new developments in pharmacology. The committee of management will be strengthened to undertake this work, and Prof. M. L. Rosenheim has agreed to act as chairman. This is a further step to implement recommendations in the reports of the Hinchliffe and Douglas Committees on the cost of prescribing in England and in Scotland.

TRAINING FOR WORK STUDY IN HOSPITALS

LAST year the Minister of Health set up a council to advise on means of improving efficiency in the National Health Service. Sir Ewart Smith, its chairman, suggested that King Edward's Hospital Fund should help in training work-study officers for the hospital service, and later the Fund offered to provide such training in its Hospital Administrative Staff College.

The tutorial staff of the staff college, under the principal, Mr. R. A. Mickelwright, is being increased by the addition of work-study technical experts. Mr. P. Torrie, who has been head of the training section of the central work-study department of Imperial Chemical Industries Ltd., will be head of the work-study team, and Mr. Geoffrey Weston, group secretary of the Reading and District Hospital Management Committee, will be associated with it part-time. The expansion of the general work of the staff college will be met by the appointment to the full-time staff of Mr. K. Osborne, at present training and personnel manager of the Corner House organisation of J. Lyons & Co. Ltd.

There is to be no diminution of the general work of the staff college at present in hand or projected. Additional premises have been bought, and three separate courses will be concurrently in residence, usually consisting of a senior officers' refresher course, a work-study course, and a training course in hospital administration. Besides the work-study training courses (which will last about twelve weeks), short work-study appreciation courses (lasting not more than one week), and the training courses under the Ministry of Health's selective recruitment and training scheme, the programme for 1961 will include separate courses in administration for physician-superintendents of mental hospitals, for clinical psychiatrists, for hospital secretaries, and for deputy secretaries of regional hospital boards. There will also be special courses in personnel relations and courses for middle-range administrative officers, and others.

The courses in work study will begin in the late autumn. Application should be made to the principal of the staff college at 2, Palace Court, Bayswater, London, W.2.

HOSPITAL BUILDING COSTS

HOSPITAL design and construction is to be investigated by the Building Research Station, under the Department of Scientific and Industrial Research, and a programme of research is now being arranged with the Ministry of Health and the Department of Health for Scotland.[1] For example, the cost of engineering services in hospitals (heating and ventilation, operating-theatre services, lighting, &c.) can amount to a third of the total building cost, and ways of providing these services more economically will be studied by the Station. Cost studies will also be carried out on recently constructed hospitals in an effort to identify other parts of the building process where economies might be achieved. It should be possible to pick out anomalies in building costs between different hospitals of similar capacity and to trace their causes.

1. Building Research 1959. Published by H.M. Stationery Office for the Department of Scientific and Industrial Research. 7s.

ANGLO-GERMAN MEDICAL SOCIETY

AT this society's annual meeting in Stuttgart on July 30 and 31, three sessions were devoted to a symposium on medical education. Prof. J. S. Mitchell, F.R.S., president of the British section, opened a discussion on undergraduate teaching. Prof. Rudolf Schoen (Göttingen) emphasised the value still attached in Germany to formal systematic lecture courses, and the difficulties in the way of a liberalisation of the curriculum. Among the guest speakers were Mr. C. J. Wright, a senior student from Glasgow University, and a German medical student from Tübingen. An account of the training of specialists in the Federal Republic led to a lively discussion. Many speakers were impressed by the need for specialist examinations corresponding to the M.R.C.P. and F.R.C.S. At present a specialist was registered after a period of training at one or more approved centres, but he may not qualify in more than one specialty, and the collecting of higher degrees was thus rendered virtually impossible. The chief difficulty in this simple method of specialist registration was the maintenance of a high and uniform standard throughout the West German Republic, and most doctors expressed themselves in favour of examinations for specialists.

Prof. H. Bennhold, of Tübingen, president of the German section, opened a discussion on the organisation of hospitals in the Federal Republic and in the National Health Service. The German members were impressed by the good relations between doctors and administrators in the N.H.S., but doubted whether such a system would be successful in the different environment of the Federal Republic. The "economic miracle" in Germany had led to the same shortage of nurses and auxiliaries as was experienced in Britain. There was a need for experimentation with home-care units and self-service wards.

Through special efforts by the publishers, Messrs. Schattauer, of Stuttgart, and by the secretaries of the society, Dr. E. Kawerau (Department of Chemical Pathology, St. Mary's Hospital, London, W.2) and Dr. F. K. Beller (Tübingen, Postfach 161), the first number of the bilingual *Anglo-German Medical Review* was completed and distributed to participants. The full text of the symposium will appear in the second number of the Review. In the opening pages of the new journal, Dr. Bennhold writes of the man who founded the *Deutsche Medizinische Wochenschrift* in 1876, Paul Boerner.

"... it can be proved that Wakley with *The Lancet* was his model. He, too, possessed a social conscience and revolutionary blood; in 1848 as a 22 years old law student he had taken part in the March Revolution on the barricades of Berlin and had felt profound disappointment over the reserved attitude of the Berlin professors. As a medical student he was a pupil of Virchow and Helmholtz. Not until the age of 52 did he start to edit the periodical. His ideal of a technical periodical was a paper which 'did not serve abstract knowledge alone, but had also set itself the task of giving a true reflection of that side of a doctor's life which is turned towards the public ... simply because doctors, as hardly any other profession, are in the midst of the people it is their right, as their duty, to take part in the things which affect the people.'"

The next annual meeting will be in London on Sept. 28–30, 1961, and will include a symposium on drug action and modern therapy.

MUSEUM OF ORTHOPÆDIC RADIOLOGY

WITH the collaboration of the Royal National Orthopædic Hospital, the Institute of Orthopædics has provided new and larger premises for its museum of orthopædic radiology. The museum contains over 10,000 films fully classified and documented, including a general section and one covering all known disorders of bones and joints. Over 10,000 doctors and others have used it in the past ten years. The collection was made by Dr. F. Campbell Golding and is constantly revised and enlarged.

The new room, which leads off the radiology department, has seating and viewing space for 10 people. Through the institute librarian, visitors may also refer to a classified and annotated collection of clinical photographs and prints of radiographs, collected since the earliest days of the Institute, and developed chiefly through the efforts of Dr. R. O. Murray.

University of Oxford

On July 30 the degree of M.B. was conferred on G. H. Foster and Peter Howard.

British Medical Association

On Thursday, Sept. 8, at 2.15 P.M., in the Lanchester Building, University of Southampton, University Road, Southampton, Dr. J. A. L. Vaughan Jones will give the Mackenzie industrial health lecture. His subject will be Rehabilitation—Theory and Practice.

Society for Social Medicine

This society will meet in St. Hugh's College, Oxford, on Sept. 29–Oct. 1. The proceedings will include a symposium on the epidemiology of leukæmia.

World Congress of Psychiatry

This congress will be held in Montreal from June 4 to 10, 1961. Further particulars may be had from the general secretary of the congress, 1025, Pine Avenue West, Montreal 2, P.Q., Canada.

International Diabetes Federation

This Federation will hold an international congress in Geneva from July 10 to 14, 1961. Further particulars may be had from the general secretary of the congress, Dr. Bernard Rilliet, 4, boulevard des Tranchées, Geneva, Switzerland.

Hungarian Congress of Internal Medicine

This congress will be held in Budapest from Nov. 23 to 26. The subject for discussion is the pathology of the kidney. Further particulars may be had from the secretariat, 2nd Department of Medicine, University Medical School of Budapest, VIII, Szentkirályi u. 46, Hungary.

Horder Centres for Arthritics

The charity known as the Horder Centres for Arthritics was founded in 1954, with the late Lord Horder as president. Its aim is to help severely disabled arthritics, both young and old. The first Horder Centres will be built upon part of a 54-acre site near Crowborough in Sussex which has just been bought.

World Health Organisation

Sir John Charles, chief medical officer of the Ministry of Health, was elected chairman of the fourth W.H.O. expert committee on public-health administration which met in Geneva on Aug. 1–6. The Minister of Health of the Republic of Russia, Dr. N. A. Vinogradov, was elected vice-chairman.

Control of Tuberculosis in Adolescence

The Chest and Heart Association is holding a symposium on this subject, on Wednesday, Sept. 28, at 2 P.M., at the London School of Hygiene and Tropical Medicine, Keppel Street, London, W.C.1. Further details may be had from the Association at Tavistock House North, W.C.1.

Conference on Mental Health

In Mental Health Year a Northern Ireland Health Services Conference has been arranged to bring together representatives of the statutory and voluntary bodies, professional and other persons, who are concerned directly or indirectly with the promotion of mental health. It will be held in the Sir William Whitla Hall, Queen's University, Belfast, on Sept. 27–29. Further details may be had from the secretary of the Northern Ireland Health Services Liaison Committee, 27, Adelaide Street, Belfast.

Preparation for Parenthood

As a result of recommendations made at the conference last March on Human Relationships in the Care of Mother and Baby, the council of the Royal College of Midwives has set up a committee "to consider the need for research into (1) such teaching as is available for parents during the antenatal and postnatal periods in preparation for parenthood and (2) whether the present teaching meets the needs of parents". Among the members are Dr. Harvey Flack, Dr. David Morris, and Prof. Norman Morris.

Royal Medical Benevolent Fund

As announced last week, the annual general meeting of the Fund will be held at 5 P.M. on Monday, Sept. 5, at the house of the Medical Society of London, 11, Chandos Street, W.1.

On Wednesday, Aug. 17, at 5.15 P.M. at the Royal Free Hospital, Gray's Inn Road, London, W.C.1, Dr. Felix Wroblewski, of New York, will speak on serum enzymes in diagnosis.

The autumn courses for physical-medicine and orthopædic consultants and senior registrars on the rehabilitation of the amputee will be held on Nov. 2–3 (physical medicine) and from Nov. 21 to 25 (orthopædic) at the Limb Fitting Centre, Queen Mary's Hospital, Roehampton, S.W.15. Applications should be made to the principal medical officer, Artificial Limbs and Appliances (Med.5 PL) at the hospital.

Selected papers from the *Korsakov Journal of Neuropathology and Psychiatry* are to be published quarterly in English, beginning with the first issue of 1960, under the editorship of Dr. W. Ritchie Russell. English abstracts of articles not translated will be included. Particulars may be had from Pergamon Press, Headington Hill Hall, Oxford.

Appointments

BURY, H. S., M.R.C.S., D.P.H.: deputy M.O.H., Bedfordshire.
CAMERON, I. A., M.B. Edin., D.P.M.: assistant psychiatrist, Crichton Royal Mental Hospital, Dumfries.
DANIEL, OWEN, M.B. Lond., F.R.C.S.: consultant in general surgery, Clwyd and Deeside H.M.C.
DUCKWORTH, G. W., M.B. Lond., F.F.A. R.C.S., D.A.: part-time consultant anæsthetist, Royal National Orthopædic Hospital, London.
HILL, D. B., M.B. Cantab., D.P.H.: assistant M.O., school health and maternal and child welfare services, Bristol.
JUKES, MARJORIE V., M.B. Lpool, D.P.H.: assistant M.O., Wirral district, Cheshire.
LAMB, E. H., M.B. Edin., D.P.H., D.I.H.: assistant M.O. and M.O.H., Caistor and Market Rasen, Lincolnshire.
MULLARD, K. S., M.B. Cantab., F.R.C.S.E.: director, thoracic and cardiac surgical services, Wessex Regional Hospital Board.
PENMAN, H. G., M.B. Cantab., M.R.C.P., D.T.M. & H.: assistant pathologist (S.H.M.O.), Portsmouth and Isle of Wight area pathological service.
SHORT, RICHARD, L.R.C.P.E., D.P.H.: senior M.O. for mental health, Edinburgh.
SUTTIE, B. R. D., M.B. St. And.: M.O., Eastern Regional Hospital Board, Scotland, as deputy to the group medical superintendent to the board of management for the Dundee General Hospitals.
TEEUWEN, J. J., M.R.C.S., D.O.M.S.: part-time chief clinical assistant (S.H.M.O.), Western Ophthalmic Hospital, London.
WALLER, W. D., M.B. Cantab.: part-time chief clinical assistant (S.H.M.O.), Western Ophthalmic Hospital, London.

Birmingham Regional Hospital Board

CAMPKIN, T. V., M.B. Lond., F.F.A. R.C.S., D.A.: part-time consultant anæsthetist, Midland centre for neurosurgery, Smethwick and United Birmingham Hospitals.
CLEOBURY, J. F., M.B. Lond., M.R.C.P., D.P.M., D.C.H.: consultant psychiatrist and deputy medical superintendent, Birmingham (mental A) group of hospitals.
JONES, L. G. G., M.R.C.P.: part-time consultant venereologist, Coventry and South Warwickshire groups of hospitals.
MACKINNON, JOHN, M.D. Sheff., M.R.C.P.: consultant cardiologist, South Warwickshire, Birmingham (Dudley Road) and (Sanatoria) groups of hospitals.
REES, E. G., M.B. Lond., M.R.C.P.: consultant pathologist, Shrewsbury group of hospitals and Robert Jones and Agnes Hunt Orthopædic Hospital.
TAYLOR, R. M., M.B. Manc., D.P.M.: consultant psychiatrist, Birmingham (mental C) group of hospitals.

Liverpool Regional Hospital Board:

MADDEN, J. S., M.B. N.U.I., M.R.C.P.E., D.P.M.: consultant psychiatrist, Deva Hospital.
PERERA, J. K. P., M.B. Cantab., F.R.C.S.E., M.R.C.O.G.: part-time consultant obstetrician and gynæcologist, North Liverpool group of hospitals.
RAWLINSON, J. K. MCC., CH.M. Lpool, F.R.C.S.: consultant general surgeon, Walton Hospital.
ROBERTS, J. R., M.D. Lpool, M.R.C.P.: part-time consultant pædiatrician, Birkenhead and North Wirral H.M.C. groups.

Newcastle Regional Hospital Board:

AZIZKHAN, R. G., M.B. Bombay, F.R.C.S.E.: senior casualty officer, South West Durham group of hospitals.
BRENNAN, J. B., M.D. Glasg., D.PHYS.MED.: assistant physician (S.H.M.O.), geriatric unit, Sunderland group of hospitals.
CAIRD, D. MCK., M.B. St. And., F.R.C.S.: consultant orthopædic surgeon, North and South Tees-side groups of hospitals.
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